(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 035 115 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
13.09.2000 Bulletin 2000/37

(21) Application number: **00102260.7**

(22) Date of filing: **15.02.2000**

(51) Int. Cl.[7]: **C07D 213/82**, C07D 213/75, C07D 401/12, C07D 401/04, C07D 213/74, C07D 213/38, C07D 213/30, C07D 413/12, A61P 25/00, A61P 29/00, A61K 31/44, A61K 31/455, A61K 31/4427

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **24.02.1999 EP 99103504**
29.11.1999 EP 99123689

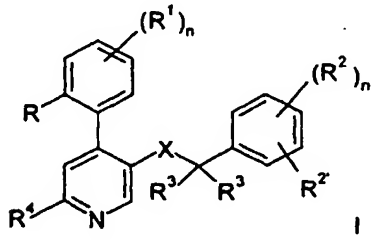
(71) Applicant:
F. HOFFMANN-LA ROCHE AG
4070 Basel (CH)

(72) Inventors:
- **Boes, Michael**
  Montreal, Quebec H2X 3P7 (CA)
- **Branca, Quirico**
  4102 Binningen (CH)
- **Galley, Guido**
  79618 Rheinfelden (DE)
- **Godel, Thierry**
  4056 Basle (CH)
- **Hoffmann, Torsten**
  4127 Birsfelden (CH)
- **Hunkeler, Walter**
  4312 Magden (CH)
- **Schnider, Patrick**
  4104 Oberwil (CH)
- **Stadler, Heinz**
  4310 Rheinfelden (CH)

(74) Representative:
Poppe, Regina et al
F.Hoffmann-La Roche AG
Patent Department(PLP),
124 Grenzacherstrasse
4070 Basel (CH)

(54) 4-Phenylpyridine derivatives and their use as NK-1 receptor antagonists

(57) The present invention relates to compounds of the general formula



I

wherein

R is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

R^1 is hydrogen or halogen; or

R and R^1 may be together -CH=CH-CH=CH-;

R^2 and $R^{2'}$ are independently from each other hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano; or

R^2 and $R^{2'}$ may be together -CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl or lower alkoxy;

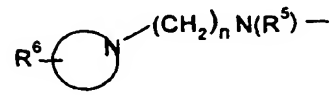
R^3 is hydrogen, lower alkyl or form a cycloalkyl group;

R^4 is hydrogen, $-N(R^5)_2$, $-N(R^5)(CH_2)_nOH$, $-N(R^5)S(O)_2$-lower alkyl, $-N(R^5)S(O)_2$-phenyl, $-N=CH-N(R^5)_2$, $-N(R^5)C(O)R^5$ or a cyclic tertiary amine of the group

EP 1 035 115 A1

(Cont. next page)

or the group



;

R^5 is, independently from each other, hydrogen, C_{3-6}-cycloalkyl, benzyl or lower alkyl;

R^6 is hydrogen, hydroxy, lower alkyl, $-(CH_2)_nCOO$-lower alkyl, $-N(R^5)CO$-lower alkyl, hydroxy-lower alkyl, cyano, $-(CH_2)_nO(CH_2)_nOH$, -CHO or a 5-or 6 membered heterocyclic group, optionally bonded via an alkylene group,

X is $-C(O)N(R^5)-$, $-(CH_2)_mO-$, $-(CH_2)_mN(R^5)-$, $-N(R^5)C(O)-$, or $-N(R^5)(CH_2)_m-$;

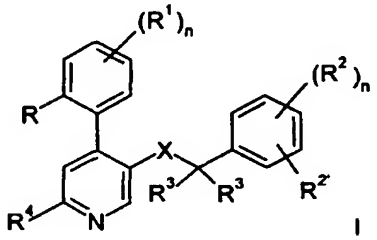
n is 0-4; and

m is 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof. The compounds of formula I show a high affinity to the NK- 1 receptor. They may be used for the treatment of diseases, which relate to NK- 1 receptor antagonists.

Description

[0001] The present invention relates to compounds of the general formula



I

wherein

R is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

R^1 is hydrogen or halogen; or

R and R^1 may be together -CH=CH-CH=CH-;

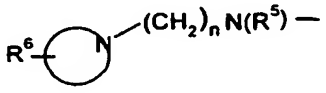
R^2 and $R^{2'}$ are independently from each other hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano; or

R^2 and $R^{2'}$ may be together -CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl or lower alkoxy;

R^3 is hydrogen, lower alkyl or form a cycloalkyl group;

R^4 is hydrogen, $-N(R^5)_2$, $-N(R^5)(CH_2)_nOH$, $-N(R^5)S(O)_2$-lower alkyl, $-N(R^5)S(O)_2$-phenyl, $-N{=}CH-N(R^5)_2$, $-N(R^5)C(O)R^5$ or a cyclic tertiary amine of the group

or the group



;

R^5 is, independently from each other, hydrogen, C_{3-6}-cycloalkyl, benzyl or lower alkyl;

R^6 is hydrogen, hydroxy, lower alkyl, $-(CH_2)_nCOO$-lower alkyl, $-N(R^5)CO$-lower alkyl, hydroxy-lower alkyl, cyano, $-(CH_2)_nO(CH_2)_nOH$, -CHO or a 5-or 6 membered heterocyclic group, optionally bonded via an alkylene group,

X is $-C(O)N(R^5)-$, $-(CH_2)_mO$, $-(CH_2)_mN(R^5)-$, $-N(R^5)C(O)-$, or $-N(R^5)(CH_2)_m-$;

n is 0-4; and

m is 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

[0002] The compounds of formula I and their salts are characterized by valuable therapeutic properties. It has been surprisingly found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor. Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The receptor for substance P is a member of the superfamily of G protein-coupled receptors.

[0003] The neuropeptide receptor for substance P(NK-1) is widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes.

The central and peripheral actions of the mammalian tachykinin substance P have been associated with numerous inflammatory conditions including migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease as well as mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 1996, 7, 187-214), anxiety (Can. J. Phys., 1997, 75, 612-621) and depression (Science, 1998, 281, 1640-1645).

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases reviewed in "Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13, 23-93, 1993.

[0004] Furthermore, Neurokinin 1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinin, in particular substance P.Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (WO 95/16679, WO 95/18124 and WO 95/23798).

[0005] The neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting.

[0006] In addition, in The New England Journal of Medicine, Vol. 340, No. 3 190-195, 1999 has been described the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.

[0007] Furthermore, US 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as NK-1 receptor antagonist.

[0008] Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts thereof, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier or in the manufacture of corresponding medicaments.

[0009] The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders or emesis by the administration of NK-1 receptor antagonists. A major depressive episode has been defined as being a period of at least two weeks during which, for most of the day and nearly every day, there is either depressed mood or the loss of interest or pleasure in all, or nearly all activities.

[0010] The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1-7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1-4 carbon atoms.

[0011] The term "lower alkoxy" denotes a group wherein the alkyl residues are as defined above, and which is attached via an oxygen atom.

[0012] The term "halogen" denotes chlorine, iodine, fluorine and bromine.

[0013] The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3-6 carbon atoms.

[0014] The term "cyclic tertiary amine" denotes, for example, pyrrol-1-yl, imidazol-1-yl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl.

[0015] The term "5 or 6 membered heterocyclic group" denotes, for example pyridinyl, pyrimidinyl, oxadiazolyl, triazolyl, tetrazolyl, thiazolyl, thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, piperazinyl or piperidyl.

[0016] The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

[0017] Exemplary preferred are compounds, in which X is -C(O)N(R^5)-, wherein R^5 is methyl, ethyl or cyclopropyl, for example the following compounds:

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-chloro-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-trifluoromethyl-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-fluoro-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-methoxy-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-phenyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-ethyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-cyclopropyl-4-o-tolyl-nicotinamide,
N-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Di-fluorobenzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Di-chlorobenzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
2'-Methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-2-carboxylic acid-(3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-naphthalen-1-yl-nicotinamide,
(4-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazin-1-yl)-acetic acid ethyl ester,
5'-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-propyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
(RS)-6-[3-(Acetyl-methyl-amino)-pyrrolidin-1-yl]-N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-thiomorpholin-4-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(1-oxo-1l 4-thiomorpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-cyanomethyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-[1,2,4] oxadiazol-3- ylmethyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[4-(5-oxo-4,5-dihydro-1H-[1,2,4] triazol-3-ylmethyl)-piperazin-1-yl]-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-formyl-piperazin-1-yl)-N-methyl-4-o - tolyl-nicotinamide and
N-Methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide.

[0018] Further preferred are compounds, in which X is -N(R^5)-CO-, wherein R^5 is hydrogen or methyl.

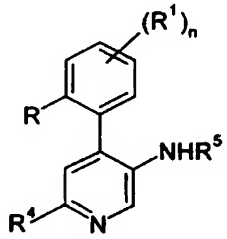
[0019] Examples of such compounds are:

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-acetamide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-propionamide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-morpholin-4-yl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-{6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-pyrimidin-2-yl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-dimethylamino-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-piperazin-1-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,

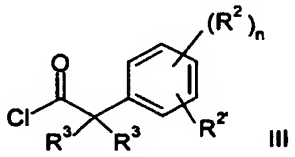
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-{6-[(2-hydroxy-ethyl)-methyl-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide,
(R)-2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-acetamide and
[2-(3,5-Bis-trifluoromethyl-phenyl)-2-methyl-propyl]-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-methyl-amine.

[0020] The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

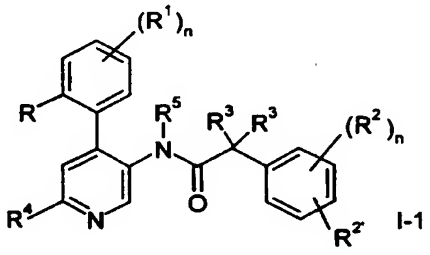
a) reacting a compound of formula


II

with a compound of formula

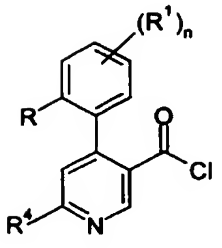

III

to a compound of formula


I-1

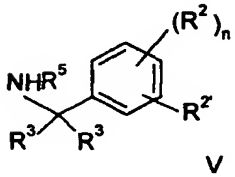
wherein R^1-R^5, R and n have the significances given above, or

b) reacting a compound of formula



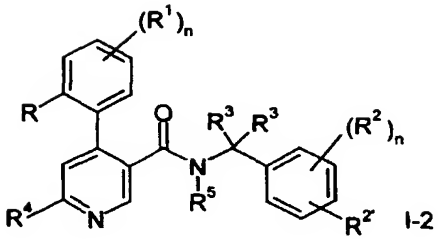
IV

with a compound of formula



V

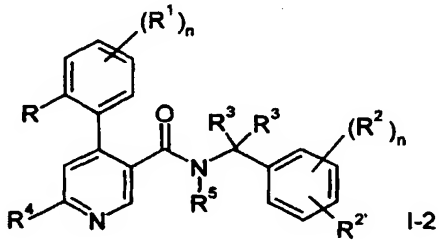
to give a compound of formula



I-2

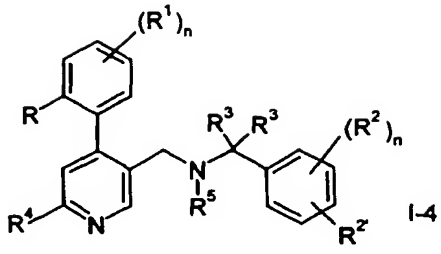
wherein R^1-R^5, R and n have the significances given above, or

c) reducing a compound of formula



I-2

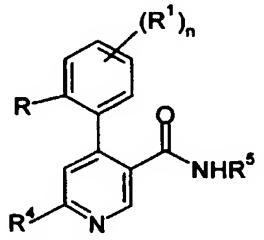
to a compound of formula



I-4

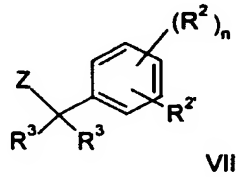
wherein the definition of substituents is given above, or

d) reacting a compound of formula



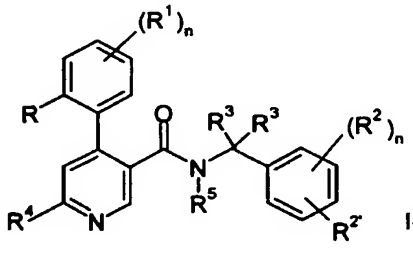
VI

with a compound of formula



VII

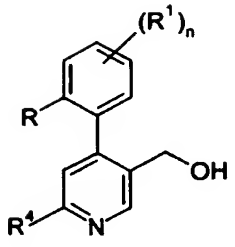
to a compound of formula



I-2

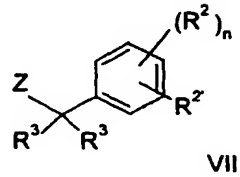
wherein Z is Cl, Br, I or $-OS(O)_2C_6H_4CH_3$ and the other definitions of substituents are given above, or

e) reacting a compound of formula



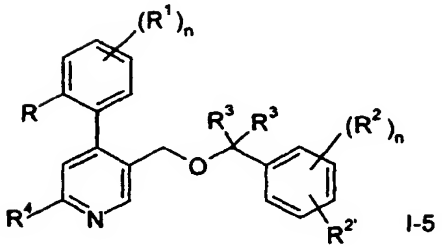
VIII

with a compound of formula



VII

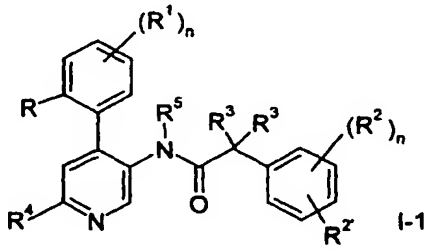
to a compound of formula



I-5

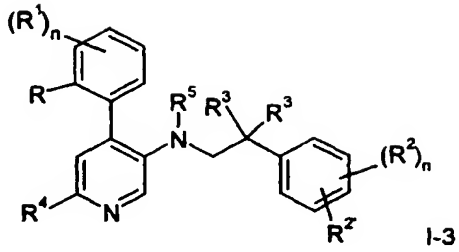
wherein Z is Cl, Br, I or $OS(O)_2C_6H_4CH_3$ and the definition of the other substituents is given above, or

f) reducing a compound of formula



I-1

to a compound of formula



I-3

wherein the definition of substituents is given above,

or

h) modifying one or more substituents R^1-R^6 or R within the definitions given above, and if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

[0021] In accordance with process variant a) DIPEA (N-ethyldiisopropyl-amine) is added to a mixture of a compound of formula II, for example methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]amine, and a compound of formula III, for example 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in dichloromethane and the mixture is stirred at temperatures between 35-40°C. The desired compound of formula I-1 is isolated after purification in good yields.

[0022] Process variant b) describes the reaction of a compound of formula IV with a compound of formula V to a compound of formula I-2. The reaction is carried out in conventional manner, for example in a solvent, such as a mixture of toluene and triethyl-amine. The mixture is refluxed for about 1 hour.

[0023] In accordance with process variant c) a compound of formula I-2 is reduced to a compound of formula I-4. This reaction is carried out with a reducing agent, such as $LiAlH_4$ or $BH_3 \cdot THF$, in conventional manner.

[0024] Process variant d) describes the reaction of a compound of formula VI with a compound of formula VII to a compound of formula I-2. This reaction is carried out by deprotonation of a compound of formula VI with KHMDS (potassium hexamethyldisilazide) and subsequent addition of a compound of formula VII. A suitable solvent is tetrahydrofuran. The reaction is carried out at room temperature.

[0025] In accordance with process variant e) a compound of formula I-5 is prepared. This reaction is carried out by deprotonation of a compound of formula VIII with NaH and susequent addition of a compound of formula VII. This reaction is carried out in conventional manner.

[0026] A further method for the preparation of a compound of formula I is described in process variant f). A compound of formula I-1 is reduced to a compound of formula I-3 in conventional manner, for example with $LiAlH_4$ or $BH_3 \cdot THF$.

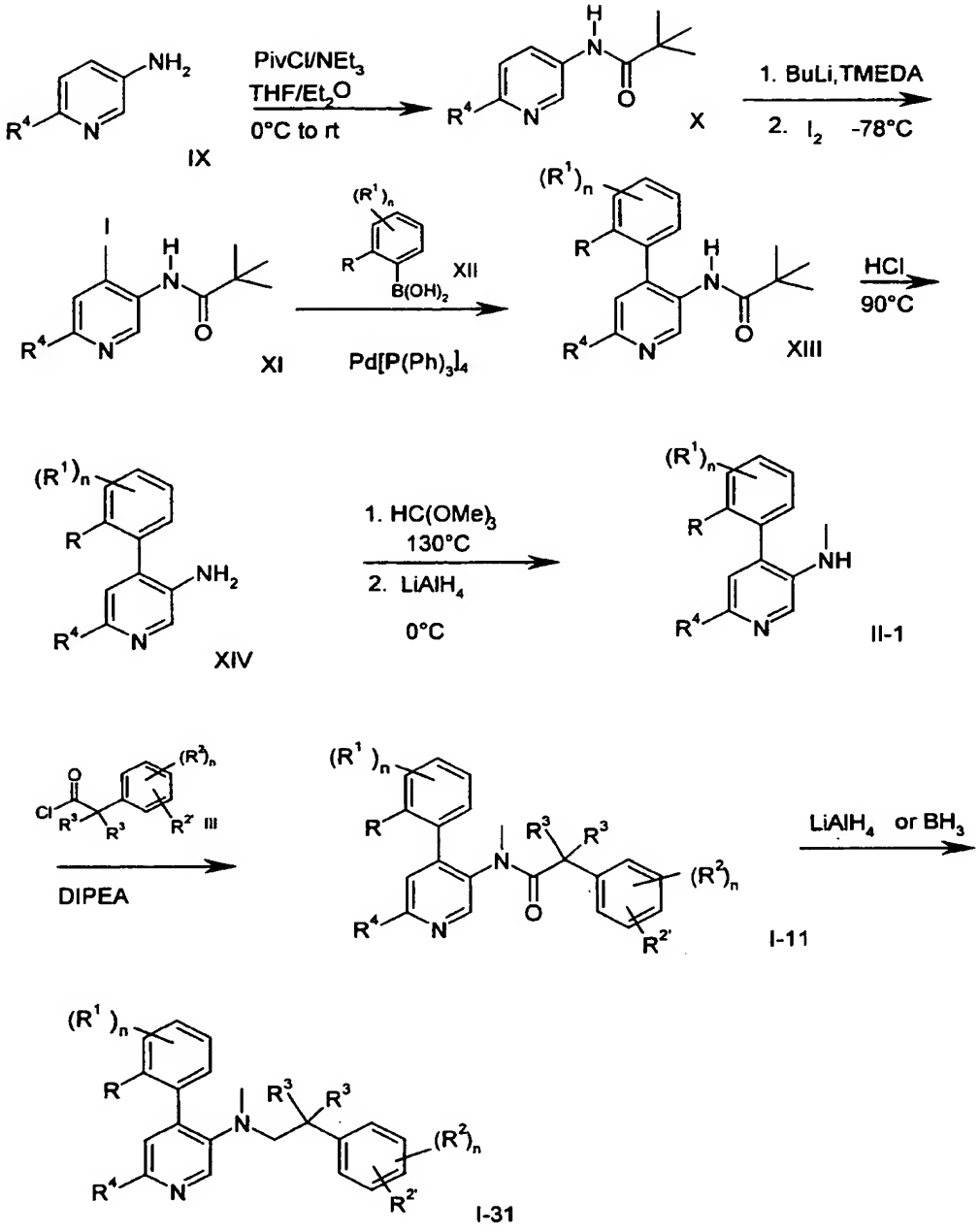
[0027] The salt formation is effected at room temperature in accordance with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates, methan-sulphonates, p-toluenesulphonates and the like are examples of such salts.

[0028] The following schemes 1-8 describe the processes for preparation of compounds of formula I in more detail. The starting materials of formulae V, IX, XII, XV, XVI, XXII, XXV, XXVIII, IXXX and XXX are known compounds and may be prepared according to methods known in the art.

[0029] In the schemes the following abbreviations have been used:

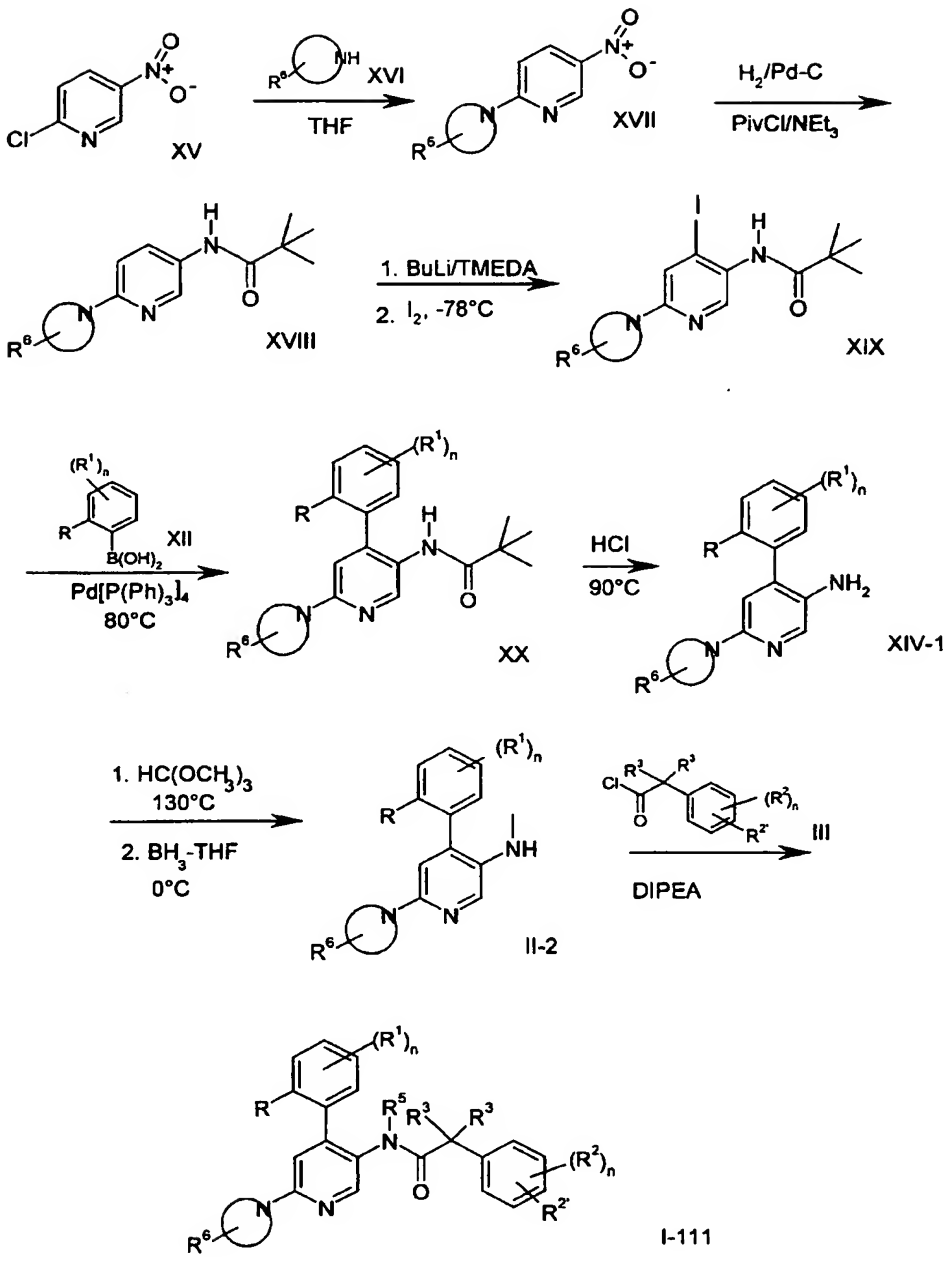
PivCl	pivaloyl chloride
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylene diamine
DIPEA	N-ethyldiisopropyl-amine
KHMDS	potassium hexamethyldisilazide

Scheme 1



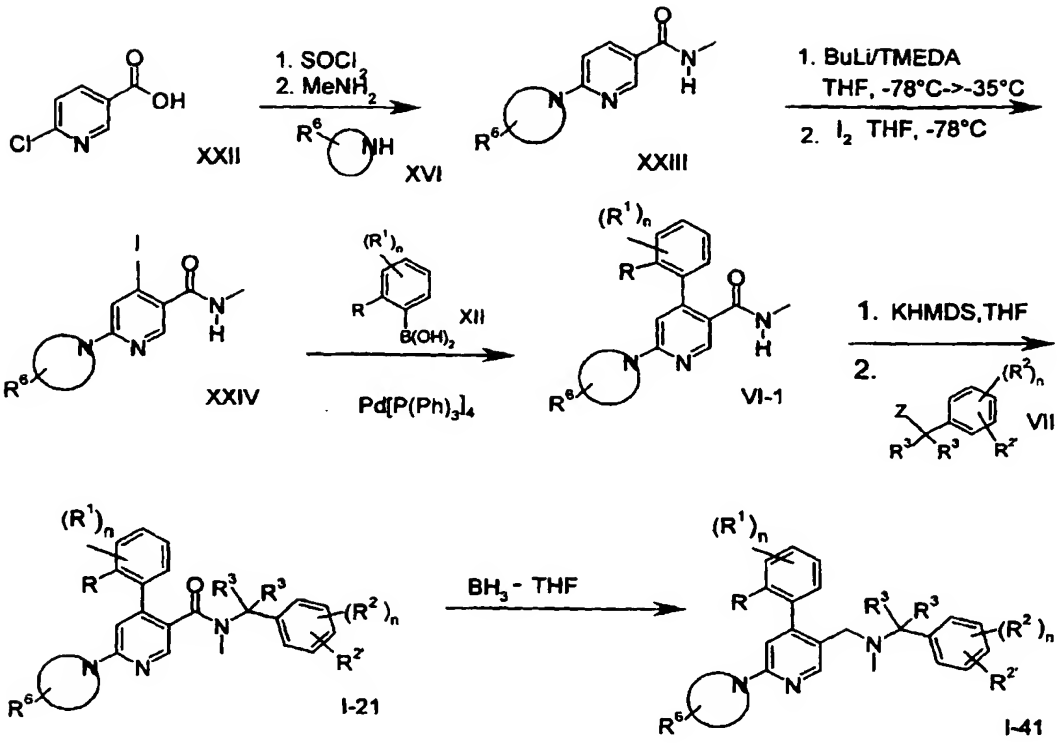
[0030] The definition of substituents is given above.

Scheme 2



[0031] The definition of substituents is given above.

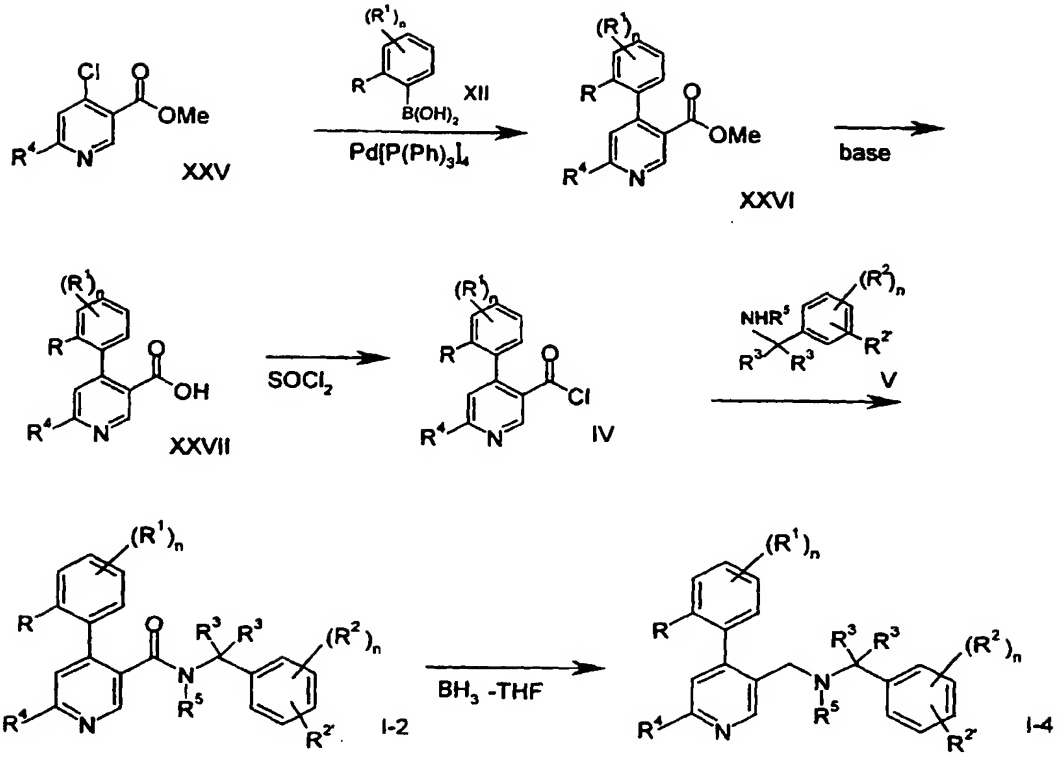
Scheme 3



Z = Cl, Br, I or $OS(O)_2C_6H_4CH_3$

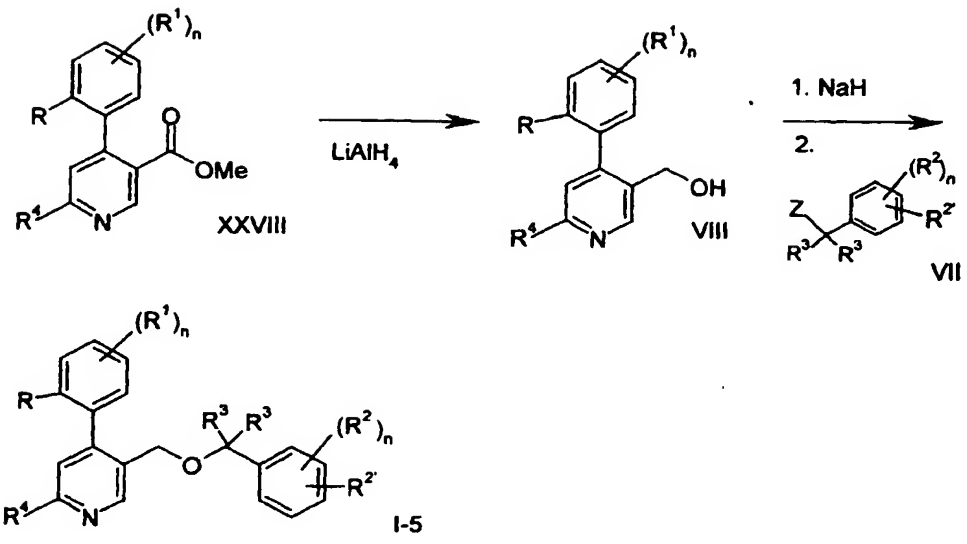
and the definition of the other substituents is given above.

Scheme 4



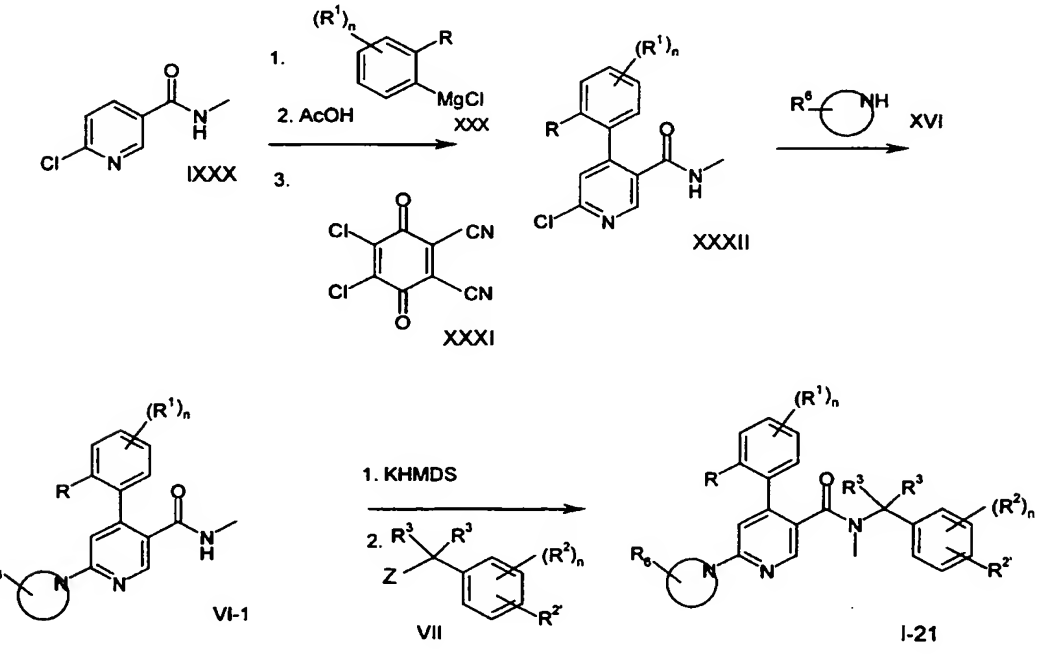
[0032] The definition of substituents is given above.

Scheme 5



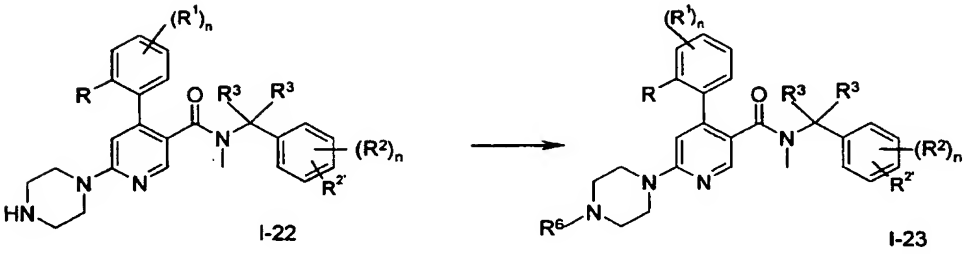
[0033] Z is Cl, Br, I or $-OS(O)_2C_6H_4CH_3$ and the definition of the other substituents is described above.

Scheme 6



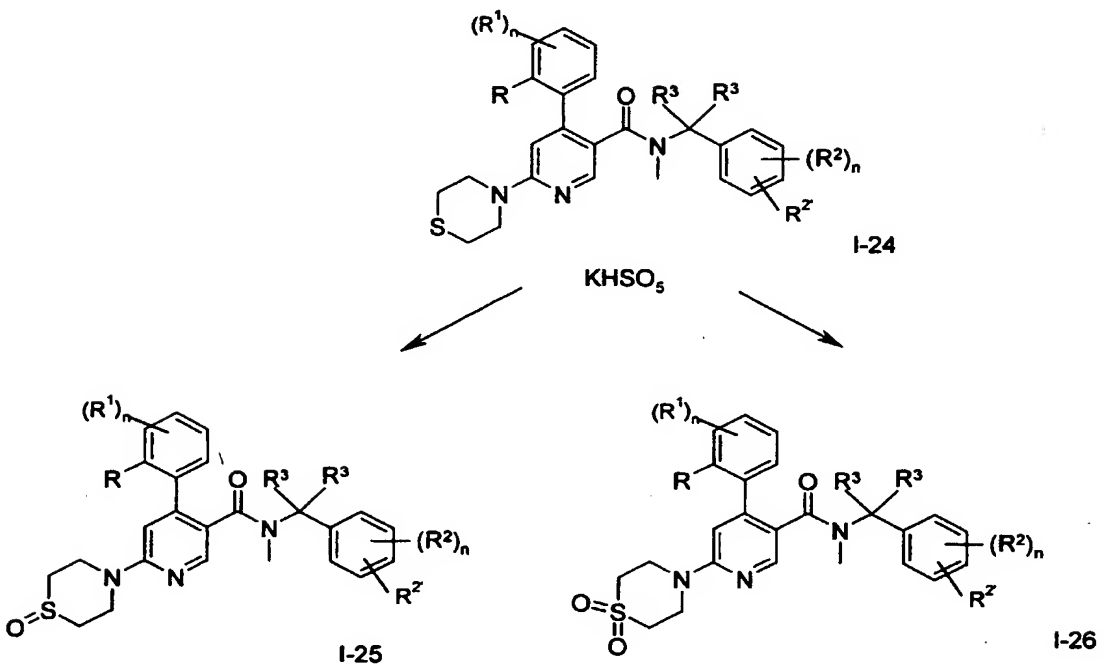
[0034] Z is Cl, Br, I or $-OS(O)_2C_6H_4CH_3$ and the definition of the other substituents is given above.

Scheme 7



[0035] The definition of substituents is given above.

Scheme 8



[0036] The definition of substituents is given above.

[0037] As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor.

[0038] The compounds were investigated in accordance with the tests given hereinafter.

[0039] The affinity of test compounds for the NK_1 receptor was evaluated at human NK_1 receptors in CHO cells

infected with the human NK_1 receptor (using the Semliki virus expression system) and radiolabelled with [^{3}H]substance P (final concentration 0.6 nM). Binding assays were performed in HEPES buffer (50 mM, pH 7.4) containing BSA (0.04 %) leupeptin (8 µg / ml), $MnCl_2$ (3mM) and phosphoramidon (2 µM). Binding assays consisted of 250 µl of membrane suspension ($1.25x10^5$ cells / assay tube), 0.125 µl of buffer of displacing agent and 125 µl of [^{3}H]substance P. Displacement curves were determined with at least seven concentrations of the compound. The assay tubes were incubated for 60 min at room temperature after which time the tube contents were rapidly filtered under vacuum through GF/C filters presoaked for 60 min with PEI (0.3%) with 2 x 2 ml washes of HEPES buffer (50 mM, pH 7.4). The radioactivity retained on the filters was measured by scintillation counting. All assays were performed in triplicate in at least 2 separate experiments.

[0040] The affinity to the NK-1 receptor, given as pKi, is in the scope of 8.00-9.80 for the preferred compounds. Examples of such compounds are

N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-(2-chloro-phenyl)-nicotinamide	8.20
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide	8.47
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-{6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-isobutyramide	8.70
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-piperazin-1-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide	9.0
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[4-(5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-ylmethyl)-piperazin-1-yl]-4-o-tolyl-nicotinamide	9.54

[0041] The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

[0042] The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

[0043] Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

[0044] Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

[0045] Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

[0046] Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

[0047] Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

[0048] The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

[0049] The following Examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

Example 1

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide

a) Methyl 4-o-tolyl-nicotinoate

[0050] A mixture of 1.2 g (6.9 mmol) methyl 4-chloronicotinoate, 20 ml dimethoxyethane, 6.4 ml 2 N sodium carbon-

ate solution, 0.4 g (0.34 mmol) tetrakis(triphenylphosphine)palladium(0) and 1.4 g (10.3 mmol) o-tolylboronic acid was heated under argon at 80°C for 18h. After cooling to room temperature, the aqueous phase was separated and washed twice with ethyl acetate. The combined organic layers were washed with 50 ml brine, dried (sodium sulfate), evaporated and dried *in vacuo*. The crude oil was subjected to column chromatography to yield 1.5 g (97%) of the title compound as an oil that crystallized upon storage at 0°C.

MS m/e (%): 227 (M^+, 15).

b) 4-o-tolyl-nicotinic acid

[0051] A solution of 1.13 g (5.0 mmol) methyl 4-o-tolyl-nicotinoate in 15 ml ethanol and 12 ml 2 N sodium hydroxide solution was heated to reflux for 1 h. The pH was adjusted to 5 and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried (sodium sulfate) and evaporated to give 1 g (94%) of the title compound as off white crystals.

M.p. 201-202°C.

c) N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide

[0052] A solution of 1 g (4.6 mmol) 4-o-tolyl-nicotinic acid in 10 ml dichloromethane and 2 drops of N,N-dimethylformamide was stirred with 1 ml (14 mmol) thionyl chloride for 2 h at room temperature. The solvent was removed and the residue was taken up in 10 ml toluene and 2 ml triethylamine. After the addition of 1.3 g (5.1 mmol) 3.5-bis-trifluorobenzyl-methyl amine the mixture was refluxed for 1 h and extracted twice with ethyl acetate and washed with sodium bicarbonate. The combined organic layers were dried (sodium sulfate) and evaporated. The crude oil was subjected to column chromatography to give 1.4 g (67%) of the title compound as an oil.

MS m/e (%): 452 (M^+, 5).

Example 2

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-chloro-phenyl)-nicotinamide

[0053] The title compound was obtained as an oil in comparable yields according to the procedures described above for the preparation of Example 1 using o-chlorophenylboronic acid instead of o-tolylboronic acid in step a).

MS m/e (%): 471 (M^+, 3).

Example 3

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-trifluoromethyl-phenyl)-nicotinamide

[0054] The title compound was obtained as an oil in comparable yields according to the procedures described above for the preparation of Example 1 using o-trifluoromethylphenylboronic acid instead of o-tolylboronic acid in step a).

MS m/e (%): 506 (M^+, 15).

Example 4

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-fluoro-phenyl)-nicotinamide

[0055] The title compound was obtained as an oil in comparable yields according to the procedures described above for the preparation of Example 1 using o-fluorophenylboronic acid instead of o-tolylboronic acid in step a).

MS m/e (%): 456 (M^+, 30).

Example 5

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-methoxy-phenyl)-nicotinamide

[0056] The title compound was obtained as an oil in comparable yields according to the procedures described above for the preparation of Example 1 using o-methoxyphenylboronic acid instead of o-tolylboronic acid in step a).

MS m/e (%): 469 ($M+H^+$, 100).

Example 6

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-phenyl-nicotinamide

[0057] The title compound was obtained as an oil in comparable yields according to the procedures described above for the preparation of Example 1 using phenylboronic acid instead of o-tolylboronic acid in step a).

MS m/e (%): 438 (M^+, 60).

Example 7

N-(3,5-Bis-trifluoromethyl-benzyl)-N-ethyl-4-o-tolyl-nicotinamide

[0058] The title compound was obtained as an oil in comparable yields according to the procedures described above for the preparation of Example 1 using 3,5-bis-trifluorobenzyl-ethyl amine instead of 3,5-bis-trifluorobenzyl-methyl amine in step c).

MS m/e (%): 465 ($M-H^-$, 3).

Example 8

N-(3,5-Bis-trifluoromethyl-benzyl)-N-cyclopropyl-4-o-tolyl-nicotinamide hydrochloride (1:0.8)

a) N-(3,5-Bis trifluoromethyl-benzyl)-N-cyclopropyl-4-o-tolyl-nicotinamide

[0059] A solution of 106 mg (0.5 mmol) 4-o-tolyl-nicotinic acid in 5 ml dichloromethane and 2 drops N,N-dimethyl-formamide was stirred with 0.1 ml (1.4 mmol) thionyl chloride for 1.5 h at room temperature. The solvent was removed and the residue was taken up in 5 ml dichloromethane and 0.3 ml triethylamine. After the addition of 155 mg (0.55 mmol) (3,5-bis-trifluoromethyl-benzyl)-cyclopropyl-amine the mixture was stirred at room temperature for 1 h and washed twice with water. The organic layer was dried (magnesium sulfate) and evaporated. The crude oil was subjected to column chromatography to give 140 mg (58%) of the title compound as an oil.

MS m/e (%): 479 (M^+, 100).

b) N-(3,5-Bis trifluoromethyl-benzyl)-N-cyclopropyl-4-o-tolyl-nicotinamide hydrochloride (1:0.8)

[0060] To a solution of 140 mg N-(3,5-bis trifluoromethyl-benzyl)-N-cyclopropyl-4-o-tolyl-nicotinamide in 1 ml diethyl ether were added 3 drops of 3 N hydrochloric acid solution in methanol. After stirring for 15 min at 0°C, the mixture was evaporated to dryness to give 100 mg (41%) of the title compound as white crystals. M.p. 174-178°C.

MS m/e (%): 479 (M^+, 100).

Example 9

N-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-N-methyl-4-o-tolyl-nicotinamide

[0061] The title compound was obtained as an oil in comparable yields according to the procedures described above for the preparation of Example 1 using 2-(3,5-bis-trifluorophenyl)ethyl-methyl amine instead of 3,5-bis-trifluorobenzyl-methyl amine in step c).

MS m/e (%): 467 ($M+H^+$, 100).

Example 10

N-(3,5-di-fluorobenzyl)-N-methyl-4-o-tolyl-nicotinamide

[0062] The title compound was obtained as a solid in comparable yields according to the procedures described above for the preparation of Example 1 using 3,5-difluorobenzyl-methyl amine instead of 3,5-bis-trifluorobenzyl-methyl amine in step c).

MS m/e (%): 353 ($M+H^+$, 100).

Example 11

N-(3,5-di-chlorobenzyl)-N-methyl-4-o-tolyl-nicotinamide

[0063] The title compound was obtained as an oil in comparable yields according to the procedures described above for the preparation of Example 1 using 3,5-dichlorobenzyl-methyl amine instead of 3,5-bis-trifluorobenzyl-methyl amine in step c).

MS m/e (%): 385 ($M+H^+$, 100), 387 ($M+H^+$, 70).

Example 12

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide hydrochloride (1:2)

a) 6-Chloro-N-methyl-nicotinamide

[0064] To 50 g (317 mmol) of 2-chloronicotinic acid was added 230 ml (3.16 mol) thionyl chloride at 0°C. After heating the mixture at reflux for 2h excess thionyl chloride was removed by distillation. The oily brown residue was dissolved in 250 ml dichloromethane. The solution was treated with methylamine gas at 0°C until no exothermic reaction was observed any longer. The resulting suspension was diluted with 1000 ml dichloromethane/water. The layers were separated and the aqueous layer extracted with three 300 ml portions of dichloromethane. Drying of the organic layer with sodium sulfate and concentration gave 53.2 g (98%) of the title compound as a light yellow solid.

MS m/e (%): 171 ($M+H^+$, 15).

b) N-Methyl-6-(4-methyl-piperazin-1-yl)-nicotinamide

[0065] A mixture of 52.0 g (30.5 mmol) 6-chloro-N-methyl-nicotinamide and 176 ml (1.58 mol) 1-methylpiperazine was heated at 100°C for 1.5h in an autoclave. After cooling to room temperature excess 1-methylpiperazine was removed by distillation. The residue was partitioned in 1000 ml dichloromethane/1 N aqueous sodium hydroxide solution. The layers were separated and the aqueous layer was extracted with three 500 ml portions of dichloromethane. Concentration and short column chromatography yielded 72.3 g (97%) of the title compound as a light brown solid.

MS m/e (%): 235 ($M+H^+$, 100).

c) 4-Iodo-N-methyl-6-(4-methyl-piperazin-1-yl)-nicotinamide

[0066] To a solution of 936 mg (3.99 mmol) N-methyl-6-(4-methyl-piperazin-1-yl)-nicotinamide and 2.46 ml (16.4 mmol) N,N,N',N'-tetramethylethylenediamine in 20 ml dry tetrahydrofuran 10 ml (16 mmol) of a 1.6 M solution of n-butyllithium in hexane were added dropwise at -78°C. After 0.5h the mixture was warmed to -35°C. Stirring was continued for 3h at that temperature. After cooling to -78°C a solution of 1.52 g (6.00 mmol) iodine in 2.5 ml tetrahydrofuran was added. The reaction mixture was allowed to warm up to room temperature overnight. The reaction mixture was quenched with 30 ml of a 20 % aqueous sodium hydrogensulfite solution at 0°C. Extraction with three 30 ml portions of ethyl acetate, drying with sodium sulfate and concentration gave 1.2 g of a brown oil. Column chromatography afforded 618 mg (43%) of the title compound.

MS m/e (%): 360 (M^+, 15).

d) N-Methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide

[0067] A suspension of 4.00 g (11.1 mmol) 4-iodo-N-methyl-6-(4-methyl-piperzin-1-yl)-nicotinamide and 642 mg (0.555 mmol) tetrakis(triphenylphosphine)palladium(0) in 60 ml toluene was dioxygenated with a stream of argon for 30 min. After addition of 11 ml of a 2 N aqueous solution of sodium carbonate and 1.66 g (12.2 mmol) o-tolylboronic acid, the mixture was heated at reflux overnight. Cooling to room temperature was followed by dilution with water and extraction with three 50 ml portions of ethyl acetate. The aqueous layer was saturated with sodium chloride and enacted with three 50 ml portions of dichloromethane. The combined organic layers were dried with sodium sulfate and concentrated. Column chromatography afforded 2.26 g (63%) of the title compound.

MS m/e (%): 324 (M^+, 5).

e) N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide hydrochloride (1:2)

[0068] To a solution of 750 mg (2.32 mmol) N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 16 ml tetrahydrofuran, 3 ml of a 1 M solution (3 mmol) of potassium hexamethyldisilazide in tetrahydrofuran was added at room temperature. After 1h, 0.43 ml (2.3 mmol) 3,5-bis(trifluoromethyl)benzyl bromide was added dropwise to the resulting suspension. The reaction was quenched with water after 1h and the mixture was extracted with three 20 ml portions of ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried with sodium sulfate and concentrated. Column chromatography gave 950 mg (74%) N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide. The white foam was dissolved in a small amount of diethyl ether and treated with 2 ml 3 N hydrochloric acid solution in diethyl ether. Concentration afforded 1.02 g (74%) of the title compound as a white solid.

MS m/e (%): 551 ($M+H^+$, 100).

Example 13

N-(3,5-Bis-trifluoromethyl-benzyl)-4-(2-chloro-phenyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-nicotinamide hydrochloride (1:2)

[0069] The title compound was prepared analogously to the preparation of Example 12 using 2-chlorophenylboronic acid instead of o-tolylboronic acid in step d).

MS m/e (%): 571 ($M+H^+$, 100)

Example 14

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide hydrochloride (1:2)

a) 1-Methyl-4-(5-nitro-pyridin-2-yl)-piperazine

[0070] To a solution of 20 g (126 mmol) of 2-chloro-5-nitropyridine in 200 ml tetrahydrofuran were added dropwise 35 ml (315 mmol) 1-methylpiperazine within 10 min. The reaction mixture was refluxed for additional 1.5h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was re-dissolved in 200 ml ethyl acetate. The organic phase was washed with 200 ml 1 N sodium bicarbonate solution, dried (magnesium sulfate) and evaporated to give 27.9 g (quantitative) of the title compound as a yellow solid.

MS m/e (%): 223 ($M+H^+$, 100).

b) 2,2-Dimethyl-N-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-propionamide

[0071] To a solution of 27.9 g (125.5 mmol) of 1-methyl-4-(5-nitro-pyridin-2-yl)-piperazine in 400 ml methanol were added 2.6 g of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature to *ca.* 45°C, 1 bar) until the theoretical amount of hydrogen was taken up (about 2h). The catalyst was filtered off and was

washed twice with 100 ml portions of methanol. The filtrate was evaporated *in vacuo* to give 28 g of a purple oil which consisted to *ca.* 90 % of the desired aniline derivative according to analysis by thin layer chromatography.

[0072] This crude product was dissolved in a mixture of 400 ml tetrahydrofuran and 100 ml diethyl ether. After cooling to 0°C, 30 ml (215 mmol) of triethylamine were added in one portion. Stirring was continued while 26 g (215 mmol) of pivaloyl chloride were added dropwise within a period of 10 min. The ice bath was removed and the reaction mixture was stirred for 1h at room temperature. Then, the solvent was removed *in vacuo* and the residue was suspended in 200 ml 1 N sodium bicarbonate solution. The product was extracted three times with 200 ml portions of dichloromethane, dried (sodium sulfate) and purified by flash chromatography to give 30 g (86%) of the title compound as pink crystals.

MS m/e (%): 277 ($M+H^+$, 100).

c) N-[4-Iodo-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-2,2-dimethyl-propionamide

[0073] A solution of 30 g (108 mmol) 2,2-dimethyl-N-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-propionamide and 58 ml (380 mmol) N,N,N',N'-tetramethylethylenediamine under argon in 650 ml tetrahydrofuran was cooled in a dry ice bath to -78°C. Within 1h, 239 ml (380 mmol) of a 1.6 N n-butyllithium solution in hexane were added dropwise. The reaction mixture was allowed to warm up to -30°C overnight. After cooling again to -78°C, 43.6 g (170 mmol) iodine dissolved in 60 ml tetrahydrofuran were added dropwise during 15 min. The dry ice bath was replaced by an ice bath and a solution of 90 g (363 mmol) sodium thiosulfate pentahydrate in 250 ml water were added within 10 min when the temperature of the reaction mixture had reached 0°C. Then, 1000 ml diethyl ether were added and the organic layer was separated. The aqueous layer was extracted twice with 500 ml dichloromethane and the combined organic layers were dried (magnesium sulfate) and evaporated. Flash chromatography gave 18.5 g (42%) of the title compound as a light brown oil which crystallized upon standing at room temperature.

MS m/e (%): 403 ($M+H^+$, 100).

d) 2,2-Dimethyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-propionamide

[0074] A mixture of 54 g (134 mmol) N-[4-iodo-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-2,2-dimethyl-propionamide, 420 ml toluene, 150 ml 2 N sodium carbonate solution, 4.63 g (3.9 mmol) tetrakis(triphenylphosphine)palladium(0) and 20.16 g (147 mmol) o-tolylboronic acid was heated under argon at 80°C for 12h. After cooling to room temperature, the aqueous phase was separated and washed twice with toluene. The combined organic layers were washed with 50 ml brine, dried (sodium sulfate), evaporated and dried *in vacuo* to yield 49 g (quantitative) of the title compound as a brown oil.

MS m/e (%): 367 ($M+H^+$, 100).

e) 6-(4-Methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-ylamine

[0075] A suspension of 56 g (152 mmol) 2,2-dimethyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-propionamide in 1300 ml 3 N hydrochloric acid solution was heated to 90-95°C overnight. The reaction mixture was cooled to room temperature, washed with three 500 ml portions diethyl ether and filtered over celite. The filtrate was diluted with 500 ml water and was adjusted to pH 7-8 by addition of 28 % sodium hydroxide solution under ice cooling. The product was extracted with four 1000 ml portions of dichloromethane. The combined organic layers were washed with 500 ml brine, dried (magnesium sulfate) and evaporated to give 35 g (82%) of the title compound as a light brown oil.

MS m/e (%): 283 ($M+H^+$, 100).

f) Methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine

[0076] A solution of 35 g (124 mmol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-ylamine in 270 ml trimethyl orthoformate and 8 drops trifluoroacetic acid was heated for 3h at 130°C. The reaction mixture was evaporated and dried *in vacuo* for 30 min. The residual oil was dissolved in 100 ml tetrahydrofuran and was added dropwise under ice cooling to 9.4 g (248 mmol) lithium aluminum hydride in 300 ml tetrahydrofuran. The reaction mixture was stirred for 1h at room temperature, cooled to 0°C again and acidified (pH 1-2) by addition of 28 % hydrochloric acid solution. After stirring for 5 min, 28 % sodium hydroxide solution was added to reach pH 10. The solution was filtered over celite, evaporated and purified by flash chromatography to give 23.6 g (64%) of the title compound as a light brown oil.

MS m/e (%): 297 ($M+H^+$, 100).

g) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide

[0077] A solution of 20 g (67.5 mmol) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine and 17.5 ml (101 mmol) N-ethyldiisopropylamine in 200 ml dichloromethane was cooled in an ice bath and a solution of 24 g (75 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 50 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40°C for 3h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 31.6 g (81%) of the title compound as white crystals. M.p. 155-157°C.

MS m/e (%): 579 ($M+H^+$, 100).

h) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide hydrochloride (1:2)

[0078] To a solution of 31.6 g (54.6 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide in 250 ml diethyl ether were added under ice cooling 60 ml 3 N hydrochloric acid solution in diethyl ether. After stirring for 15 min at 0°C, the suspension was evaporated to dryness, re-suspended in 100 ml diethyl ether, filtered and dried *in vacuo* to give 34.8 g (98%) of the title compound as white crystals. M.p. 235-238°C.

MS m/e (%): 579 ($M+H^+$, 100).

Example 15

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide hydrochloride (1:2)

[0079] The title compound was obtained as white crystals in comparable fields according to the procedures described above for the preparation of Example 14 using o-chlorophenylboronic acid instead of o-tolylboronic acid in step d).

MS m/e (%): 599 ($M+H^+$, 100), 601 ($M+H^+$, 43).

Example 16

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide hydrochloride (1:2)

[0080] The title compound was obtained as white crystals in comparable fields according to the procedures described above for the preparation of Example 14 using 4-fluoro-2-methylphenylboronic acid instead of o-tolylboronic acid in step d).

MS m/e (%): 597 ($M+H^+$, 100).

Example 17

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide hydrochloride (1:1)

a) 2,2-Dimethyl-N-(4-iodo-pyridin-3-yl)-acetamide

[0081] A solution of 91 g (510 mmol) N-3-pyridylpivalamide and 230 ml (1.53 mol) N,N,N',N'-tetramethylethylenediamine under argon in 2000 ml tetrahydrofuran was cooled in a dry ice bath to -78°C. Within 1h, 153 ml (1.53 mmol) of a 10 N n-butyllithium solution in hexane were added dropwise. The reaction mixture was stirred at 0°C for additional 2h. After cooling again to -78°C, 380 g (1.5 mol) iodine dissolved in 300 ml tetrahydrofuran were added dropwise during

1.5h. The dry ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight. Stirring was continued and 1000 ml water and 1000 ml saturated sodium thiosulfate pentahydrate solution were added. The aqueous layer was separated and extracted twice with 800 ml ethyl acetate. The combined organic layers were dried (magnesium sulfate) and evaporated. Chromatographical filtration gave 75 g (48%) of the title compound as brown crystals.

MS m/e (%): 305 ($M+H^+$, 100).

b) N-[4-(2-Chloro-phenyl)-pyridin-3-yl]-2,2-dimethyl-propionamide

[0082] A mixture of 35 g (115 mmol) 2,2-dimethyl-N-(4-iodo-pyridin-3-yl)-acetamide, 400 ml toluene, 120 ml 2 N sodium carbonate solution, 4.0 g (3.5 mmol) tetrakis(triphenylphosphine)palladium(0) and 20.0 g (128 mmol) o-chlorophenylboronic acid was heated under argon at 80°C for 12h. After cooling to room temperature, the aqueous phase was separated and washed twice with toluene. The combined organic layers were washed with 50 ml brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to yield 21.6 g (65%) of the title compound as white crystals.

MS m/e (%): 289 ($M+H^+$, 100), 291 ($M+H^+$, 40).

c) 4-(2-Chloro-phenyl)-pyridin-3-ylamine

[0083] A suspension of 22.2 g (77 mmol) N-[4-(2-chloro-phenyl)-pyridin-3-yl]-2,2-dimethyl-propionamide in 730 ml 3 N hydrochloric acid solution was heated to 90-95°C overnight. The reaction mixture was cooled to room temperature, washed with three 130 ml portions diethyl ether and 500 ml ethyl acetate were added. The aqueous phase was adjusted to pH 7-8 by addition of 28 % sodium hydroxide solution under ice cooling. The organic phase was separated and the product was extracted with three 200 ml portions of ethyl acetate. The combined organic layers were dried (magnesium sulfate) and evaporated to give 14.9 g (95%) of the title compound as white crystals.

MS m/e (%): 205 ($M+H^+$, 100), 207 ($M+H^+$, 39).

d) [4-(2-Chloro-phenyl)-pyridin-3-yl]-methyl-amine

[0084] A solution of 14.9 g (72.8 mmol) 4-(2-chloro-phenyl)-pyridin-3-ylamine in 80 ml trimethyl orthoformate and 5 drops trifluoroacetic acid was heated for 2.5h at 130°C. The reaction mixture was evaporated and dried *in vacuo* for 30 min. The residual oil was dissolved in 130 ml tetrahydrofuran and 220 ml (220 mmol) of 1 M borane-tetrahydrofuran complex were added dropwise under ice cooling. After stirring overnight at room temperature, the reaction mixture was evaporated, cooled to 0°C and 130 ml 5 N hydrochloric acid solution in ethanol were added carefully. The solution was refluxed for 1h, cooled to room temperature again and crushed ice was added. The aqueous phase was washed with three 100 ml portions diethyl ether and the organic layers were extracted with 100 ml 1 N hydrochloric acid solution. The combined aqueous layers were adjusted to pH 8-9 by addition of concentrated sodium hydroxide solution and were extracted with three 500 ml portions ethyl acetate. The combined organic extracts were dried (magnesium sulfate), evaporated and the solid residue was recrystallized from hexane/ethyl acetate to give 12.3 g (77%) of the title compound as white crystals.

MS m/e (%): 219 ($M+H^+$, 100), 221 ($M+H^+$, 42).

e) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide

[0085] A solution of 12.2 g (55.8 mmol) [4-(2-chloro-phenyl)-pyridin-3-yl]-methyl-amine and 15.3 ml (89 mmol) N-ethyldiisopropylamine in 130 ml dichloromethane was cooled in an ice bath and a solution of 19 g (59.6 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 30 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40°C for 20h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 24.7 g (88%) of the title compound as white crystals.

MS m/e (%): 501 ($M+H^+$, 100), 503 ($M+H^+$, 36).

f) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide hydrochloride (1:1)

[0086] To a solution of 24.7 g (54.6 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in 100 ml diethyl ether were added under ice cooling 60 ml 3 N hydrochloric acid solution in diethyl ether. After stirring for 20 min at 0°C, the suspension was evaporated to dryness, re-suspended in 100 ml diethyl ether, filtered and dried *in vacuo* to give 26.3 g (99%) of the title compound as white crystals. M.p. 186-188°C.

MS m/e (%): 501 ($M+H^+$, 100), 503 ($M+H^+$, 36).

Example 18

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide hydrochloride (1:1)

[0087] The title compound was obtained as white crystals in comparable yields according to the procedures described above for the preparation of example 17 using o-tolylboronic acid instead of o-chlorophenylboronic acid in step b).

MS m/e (%): 480 (M^+, 5), 255 (25), 225 (100).

Example 19

2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide

[0088] The title compound was obtained as a brown oil in comparable yields according to the procedures described above for the preparation of Example 17 using o-tolylboronic acid instead of o-chlorophenylboronic acid in step b). Step d) was skipped and no hydrochloride salt was prepared.

MS m/e (%): 467 ($M+H^+$, 100).

Example 20

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-acetamide hydrochloride (1:1)

[0089] The title compound was obtained in comparable yields according to the procedures described above for the preparation of Example 17 using o-tolylboronic acid instead of o-chlorophenylboronic add in step b). Step e) was performed as follows:

[0090] To a solution of 511 mg (1.88 mmol) 3,5-bis(trifluoromethyl)phenylacetic acid in 8 ml tetrahydrofuran at 0°C were added 305 mg (1.88 mmol) 1,1'-carbonyldiimidazole in one portion. The reaction mixture was stirred for 2h at room temperature and 310 mg (1.56 mmol) methyl-(4-o-tolyl-pyridin-3-yl)-amine were added. Stirring was continued at 55°C overnight. The reaction mixture was evaporated and the residue was purified by flash chromatography. The hydrochloride salt formation was performed as described in f) and gave 290 mg (38%) of the title compound as yellow crystals.

MS m/e (%): 453 ($M+H^+$, 100).

Example 21

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-propionamide hydrochloride (1:1)

[0091] The title compound was obtained as white crystals in comparable yields according to the procedures described above for the preparation of Example 17 using o-tolylboronic acid instead of o-chlorophenylboronic acid in step b) and using 2-(3,5-bis-trifluoromethyl-phenyl)-propionyl chloride instead of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in step e).

MS m/e (%): 466 (M^+, 5), 241 (12), 225 (100).

Example 22

1-(3,5-Bis-trifluoromethyl-phenyl)-cyclopropanecarboxylic acid [4-(2-chloro-phenyl)-pyridin-3-yl]-methyl-amide hydrochloride

a) 1-(3,5-Bis-trifluoromethyl-phenyl)-cyclopropanecarboxylic acid [4-(2-chlorophenyl)-pyridin-3-yl]-methyl-amide

[0092] To a solution of 88 mg (0.4 mmole) 4-(2-chloro-phenyl)-pyridin-3-yl]-methyl-amine and 0.11 ml (0.6 mmole) N-ethyldiisopropylamine in 4 ml dichloromethane was added a solution of 174 mg (0.3 mmole) 1-(3,5-bis-trifluoromethyl-phenyl)-cyclopropanecarboxylic acid chloride in 1 ml dichloromethane. After refluxing for 72 h the reaction mixture was washed twice with water, dired (magnesium sulfate) and evaporated. Chromatography of the residue (silicagel, ethyl acetate:hexane 7:3) afforded 132 mg (66%) of the title compound as a yellow oil.

MS m/e (%): 499 (M+H,100).

b) 1-(3,5-Bis-trifluoromethyl-phenyl)-cyclopropanecarboxylic acid [4-(2-chloro-phenyl)-pyridin-3-yl]-methyl-amide hydrochloride

[0093] To 125 mg 1-(3,5-bis-trifluoromethyl-phenyl)-cyclopropanecarboxylic acid [4-(2-chloro-phenyl)-pyridin-3-yl]-methyl-amide were added 1.5 ml 3 N hydrochloric acid in methanol. After evaporating the solution 3 ml ether were added and the suspension was stirred for 1 h at 0°C Filtration afforded 100 mg (75%) of the title compound as white crystals. Mp.: 194-196°C.

Example 23

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide hydrochloride (1:1.45)

a) 4-(5-Nitro-2-pyridyl)-morpholine

[0094] To a solution of 20 g (126 mmol) of 2-chloro-5-nitropyridine in 150 ml tetrahydrofuran were added dropwise 27 ml (315 mmol) morpholine within 10 min. The reaction mixture was refluxed for additional 2h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was re-dissolved in 200 ml ethyl acetate. The organic phase was washed with 200 ml 1 N sodium bicarbonate solution, dried (magnesium sulfate) and evaporated to give 27.3 g (quantitative) of the title compound as a yellow solid. M.p. 142-143°C.

b) 2,2-Dimethyl-N-(6-morpholin-4-yl-pyridin-3-yl)-propionamide

[0095] To a solution of 27.3 g (126 mmol) of 4-(5-nitro-2-pyridyl)-morpholine in 600 ml methanol were added 2.5 g of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature to *ca.* 45°C, 1 bar) until the theoretical amount of hydrogen was taken up (about 3h). The catalyst was filtered off and was washed twice with 100 ml portions of methanol. The filtrate was evaporated *in vacuo* to give 22.6 g of a purple oil which consisted to *ca.* 95 % of the desired aniline derivative according to analysis by thin layer chromatography.

[0096] This crude product was dissolved in a mixture of 240 ml tetrahydrofuran and 60 ml diethyl ether. After cooling to 0°C, 26 ml (189 mmol) of triethylamine were added in one portion. Stirring was continued while 23 g (189 mmol) of pivaloyl chloride were added dropwise within a period of 10 min. The ice bath was removed and the reaction mixture was stirred for 1h at room temperature. Then, the solvent was removed *in vacuo* and the residue was suspended in 200 ml 1 N sodium bicarbonate solution. The product was extracted three times with 200 ml portions of dichloromethane, dried (sodium sulfate) and evaporated. Recrystallization of the solid residue from ethyl acetate/hexane 1:8 gave 28.6 g (86%) of the title compound as white crystals.

MS m/e (%): 264 ($M+H^+$, 100).

c) N-(4-Iodo-6-morpholin-4-yl-pyridin-3-yl)-2,2-dimethyl-propionamide

[0097] A solution of 28.4 g (108 mmol) 2,2-dimethyl-N-(6-morpholin-4-yl-pyridin-3-yl)-propionamide and 49 ml (324 mmol) N,N,N',N'-tetramethylethylenediamine under argon in 600 ml tetrahydrofuran was cooled in a dry ice bath to -78°C. Within 1h, 202 ml (324 mmol) of a 1.6 N n-butyllithium solution in hexane were added dropwise. The reaction mix-

ture was allowed to warm up to -35°C overnight. After cooling again to -78°C, 37 g (146 mmol) iodine dissolved in 60 ml tetrahydrofuran were added dropwise during 15 min. The dry ice bath was replaced by an ice bath and a solution of 90 g (363 mmol) sodium thiosulfate pentahydrate in 250 ml water were added within 10 min when the temperature of the reaction mixture had reached 0°C. Then, 1000 ml diethyl ether were added and the organic layer was separated. The aqueous layer was extracted twice with 500 ml dichloromethane and the combined organic layers were dried (magnesium sulfate) and evaporated. Flash chromatography gave 15.6 g (37%) of the title compound as a light brown oil which crystallized upon standing at room temperature.

MS m/e (%): 389 (M^+, 71), 358 (25), 304 (43), 57 (100).

d) 2,2-Dimethyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-propionamide

[0098] A mixture of 3.50 g (9.0 mmol) N-(4-iodo-6-morpholin-4-yl-pyridin-3-yl)-2,2-dimethyl-propionamide, 35 ml toluene, 18 ml 2 N sodium carbonate solution, 312 mg (0.27 mmol) tetrakis(triphenylphosphine)palladium(0) and 1.34 g (9.9 mmol) o-tolylboronic acid was heated under argon at 80°C for 12h. After cooling to room temperature, the aqueous phase was separated and washed twice with ethyl acetate. The combined organic layers were washed with 50 ml brine, dried (sodium sulfate) and evaporated. Purification by flash-chromatography gave 3.23 g (quantitative) of the title compound as a white foam.

MS m/e (%): 354 ($M+H^+$, 100).

e) 6-Morpholin-4-yl-4-o-tolyl-pyridin-3-ylamine

[0099] A suspension of 2.93 g (8.28 mmol) 2,2-dimethyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-propionamide in 80 ml 3 N hydrochloric acid solution and 5 ml 1-propanol was heated to 90-95°C overnight. The reaction mixture was cooled to room temperature, washed with three 20 ml portions diethyl ether and filtered over celite. The filtrate was diluted with 20 ml water and was adjusted to pH 7-8 by addition of 28 % sodium hydroxide solution under ice cooling. The product was extracted with four 100 ml portions of dichloromethane. The combined organic layers were washed with 50 ml brine, dried (magnesium sulfate) and evaporated to give 2.31 g (quantitative) of the title compound as a white foam.

MS m/e (%): 269 (M^+, 100).

f) Methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine

[0100] A solution of 2.24 g (8.3 mmol) 6-morpholin-4-yl-4-o-tolyl-pyridin-3-ylamine in 17 ml trimethyl orthoformate and 3 drops trifluoroacetic acid was heated for 2h at 130°C. The reaction mixture was evaporated and dried *in vacuo* for 30 min. The residual oil was dissolved in 5 ml tetrahydrofuran and was added dropwise under ice cooling to 630 mg (16.6 mmol) lithium aluminum hydride in 20 ml tetrahydrofuran. The reaction mixture was stirred for 1h at room temperature, cooled to 0°C again and acidified (pH 1-2) by addition of 28 % hydrochloric add solution. After stirring for 5 min, 28 % sodium hydroxide solution was added to reach pH 10. The solution was filtered over celite, evaporated and purified by flash chromatography to give 1.56 g (66%) of the title compound as a white foam.

MS m/e (%): 283 (M^+, 100).

g) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide

[0101] A solution of 1.46 g (5.15 mmol) methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine and 1.32 ml (7.73 mmol) N-ethyldiisopropylamine in 15 ml dichloromethane was cooled in an ice bath and 1.8 g (5.67 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride were added dropwise. The reaction mixture was warmed to 35-40°C for 3h, cooled to room temperature again and was stirred with 25 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 2.9 g (quantitative) of the title compound as white crystals. M.p. 131-132°C.

h) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide hydrochloride (1:1.45)

[0102] To a solution of 2.9 g (5.13 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide in 50 ml diethyl ether were added under ice cooling 2.8 ml 3 N hydrochloric acid solution in diethyl ether. After stirring for 15 min at 0°C, the suspension was evaporated to dryness, re-suspended in 100 ml diethyl ether, filtered and dried *in vacuo* to give 2.82 g (89%) of the title compound as white crystals.

MS m/e (%): 566 ($M+H^+$, 100), 588 ($M+Na^+$, 11).

Example 24

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-morpholin-4-yl-pyridin-3-yl]-N-methyl-isobutyramide hydrochloride (1:1)

[0103] The title compound was obtained as white crystals in comparable yields according to the procedures described above for the preparation of Example 23 using 2-chlorophenylboronic acid instead of o-tolylboronic acid in step d).

MS m/e (%): 586 ($M+H^+$, 100).

Example 25

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-{6-(methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-isobutyramide

[0104] The title compound was obtained as light brown oil in comparable yields according to the procedures described above for the preparation of Example 23 using 4-[2-(methylamino)ethyl]-morpholine instead of morpholine in step a). No hydrochloride salt was prepared.

MS m/e (%): 623 ($M+H^+$, 100).

Example 26

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-pyrimidin-2-yl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide

[0105] The title compound was obtained as colourless oil in comparable yields according to the procedures described above for the preparation of Example 23 using 2-(1-piperazinyl)pyrimidine instead of morpholine in step a). No hydrochloride salt was prepared.

MS m/e (%): 643 ($M+H^+$, 100).

Example 27

2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide

[0106] The title compound was obtained as white powder in comparable yields according to the procedures described above for the preparation of Example 23 but step f) was skipped and no hydrochloride salt was prepared.

MS m/e (%): 552 ($M+H^+$, 100).

Example 28

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4'-(2-chloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl]-N-methyl-isobutyramide hydrochloride (1:1)

[0107] The title compound was obtained as a white powder in comparable yields according to the procedures

described above for the preparation of Example 23 using piperidine instead of morpholine in step a) and using 2-chlorophenylboronic acid instead of o-tolylboronic acid in step d).

MS m/e (%): 583 (M^+, 20), 296 (78), 255 (100).

Example 29

2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-dimethylamino-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide

[0108] The title compound was obtained as white solid in comparable yields according to the procedures described above for the preparation of Example 23 using dimethylamine hydrochloride instead of morpholine in step a). No hydrochloride salt was prepared. M.p. 174-175°C.

MS m/e (%): 524 ($M+H^+$, 100).

Example 30

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-dimethylamino-pyridin-3-yl]-isobutyramide

[0109] The title compound was obtained as white solid in comparable yields according to the procedures described above for the preparation of Example 23 using dimethylamine hydrochloride instead of morpholine in step a) and using 2-chlorophenylboronic acid instead of o-tolylboronic acid in step d). No hydrochloride salt was prepared. M.p. 162-163°C.

MS m/e (%): 544 ($M+H^+$, 100).

Example 31

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-piperazin-1-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide

[0110] To a solution of 100 mg (0.173 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide (example 14 g) and 7 mg (0.035 mmol) 1,8-bis(dimethylamino)naphthalene in 1 ml 1,2-dichloroethane at 0°C were added 26 mg (0.181 mmol) 1-chloroethyl chloroformate. After heating the reaction mixture for 1h at 80°C the solvent was removed *in vacuo* and the intermediate was purified by flash chromatography, re-dissolved in 1 ml methanol and refluxed for 3h. Flash chromatography gave 56 mg (57%) of the title compound as white foam.

MS m/e (%): 565 ($M+H^+$, 100).

Example 32

2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-N-methyl-isobutyramide

[0111] The title compound was obtained as white foam in comparable yields according to the procedures described above for the preparation of Example 23 using 4-hydroxypiperidine instead of morpholine in step a). No hydrochloride salt was prepared.

MS m/e (%): 580 ($M+H^+$, 100).

Example 33

2-(3,5-Bis-trifluoromethyl-phenyl)-N-{6-[(2-hydroxy-ethyl)-methyl-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide

[0112] The title compound was obtained as white foam in comparable yields according to the procedures described above for the preparation of Example 23 using N-methylethanolamine instead of morpholine in step a). No hydrochloride salt was prepared.

MS m/e (%): 554 ($M+H^+$, 100).

Example 34

(R)-2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

[0113] The title compound was obtained as white foam in comparable yields according to the procedures described above for the preparation of Example 23 using (R)-3-hydroxypyrrolidine instead of morpholine in step a). No hydrochloride salt was prepared.

MS m/e (%): 566 ($M+H^+$, 100).

Example 35

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-acetamide

[0114] To a solution of 300 mg (1.1 mmol) 3,5-bis(trifluoromethyl)-phenylacetic acid in 7 ml N,N-dimethylformamide were added 185 mg (1.14 mmol) 1,1'-carbonyl-diimidazole and the solution was stirred for 30 min at room temperature. After addition of 283 mg (1 mmol) of methyl-(6-morpholin-4-yl-4-tolyl-pyridin-3-yl)-amine (as described in step f) for the preparation of Example 23), the reaction mixture was heated over night at 90°C. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was re-dissolved in 30 ml ethyl acetate. The organic phase was washed with water (2 x 30 ml), brine, dried (magnesium sulfate) and evaporated. Flash chromatography gave 506 mg (94%) of the title compound as a light brown foam.

MS m/e (%): 538 ($M+H^+$, 100).

Example 36

2-(3,5-Dimethoxy-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-acetamide

[0115] To a solution of 226 mg (1.15 mmol) 3,5-dimethoxy-phenylacetic acid in 7 ml N,N-dimethylformamide were added 244 mg (1.5 mmol) 1,1'-carbonyl-diimidazole and the solution was stirred for 30 min at room temperature. After addition of 283 mg (1 mmol) of methyl-(6-morpholin-4-yl-4-tolyl-pyridin-3-yl)-amine (as described in step f) for the preparation of Example 23), the reaction mixture was heated at 70°C for 7h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was re-dissolved in 30 ml ethyl acetate. The organic phase was washed with water (2 x 30 ml), brine, dried (magnesium sulfate) and evaporated. Flash chromatography gave 347 mg (75%) of the title compound as a white foam.

MS m/e (%): 462 ($M+H^+$, 100).

Example 37

2-(3-Fluoro-5-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-acetamide

[0116] To a solution of 266 mg (1.2 mmol) 3-fluoro-5-trifluoromethyl-phenylacetic acid in 7 ml N,N-dimethylformamide were added 195 mg (1.2 mmol) 1,1'-carbonyl-diimidazole and the solution was stirred for 30 min at room temperature. After addition of 283 mg (1 mmol) of methyl-(6-morpholin-4-yl-4-tolyl-pyridin-3-yl)-amine (as described in step f) for the preparation of Example 23), the reaction mixture was heated at 90°C for 6h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was re-dissolved in 30 ml ethyl acetate. The organic phase was washed with water (2 x 30 ml), brine, dried (magnesium sulfate) and evaporated. Flash chromatography gave 432 mg (88%) of the title compound as a light yellow foam.

MS m/e (%): 488 ($M+H^+$, 100).

Example 38

[2-(3,5-Bis-trifluoromethyl-phenyl)-2-methyl-propyl]-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-methyl-amine hydrochloride (1:3)

[0117] To a mixture of 400 mg (0.60 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide hydrochloride (1:2) (example 16) and 50 ml dichloromethane were added 20 ml 1 N sodium hydroxide solution. After shaking for 1 min, the organic phase was separated and evaporated to dryness. The residue was re-dissolved in 5 ml tetrahydrofuran and 4 ml of a 1 M borane tetrahydrofuran complex solution were added. After heating at 60°C for 3 days, 10 ml 3 N hydrochloric add solution in diethyl ether were added and the reaction mixture was refluxed for 4h. The reaction mixture was cooled to room temperature, washed with 10 ml 1 N sodium hydroxide solution, dried (sodium sulfate) and purified by flash chromatography to yield 279 mg of a pale yellow oil which was transformed into the hydrochloride salt as described in step h) for the preparation of Example 23 to give 153 mg (37%) of the title compound as pale yellow crystals.

MS m/e (%): 583 ($M+H^+$, 100).

Example 39

(3,5-Bis-trifluoromethyl-benzyl)-methyl-(4-o-tolyl-pyridin-3-ylmethyl)-amine

[0118] Lithium aluminum hydride (107 mg, 2.82 mmol, 3 eq) was suspended in 7 ml tetrahydrofuran at 0°C under argon. N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide (example 1, 425 mg, 0.94 mmol), dissolved in 4 ml tetrahydrofuran, was slowly added at ~5°C. The mixture was stirred 5 min at room temperature and 1 hr under reflux.

[0119] Ethyl acetate (1 ml) was added, then the mixture was cooled to room temperature and aqueous saturated sodium sulfate solution was added dropwise. The mixture was dried (sodium sulfate), filtered, concentrated and purified by flash chromatography to give 93 mg (23%) of the title compound as a colourless oil.

MS m/e (%): 439 ($M+H^+$, 100).

Example 40

3-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-o-tolyl-pyridine

a) (4-o-Tolyl-pyridin-3-yl)-methanol

[0120] Lithium aluminum hydride (439 mg, 11.6 mmol, 1 eq) was suspended in 23 ml tetrahydrofuran at 0°C under argon. 4-o-Tolyl-nicotinic acid methyl ester (2.63 g, 11.6 mmol), dissolved in 12 ml tetrahydrofuran, was slowly added at ~5°C. The mixture was stirred 5 min at room temperature and 1h under reflux.

[0121] Ethyl acetate (1 ml) was added, then the mixture was cooled to room temperature and aqueous saturated sodium sulfate solution was added dropwise. The mixture was dried (sodium sulfate), filtered, concentrated and purified by flash chromatography to give 0.77g (33%) of the title compound as a pale yellow liquid.

[0122] Starting material (1.60 g, 61%) was recovered.

MS m/e (%): 199 (M^+, 3), 180 (100)

b) 3-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-o-tolyl-pyridine

[0123] Sodium hydride (89.1 mg, 2.04 mmol, 1.1 eq) was washed twice with n-hexane under argon and suspended in 1 ml dimethyl formamide. (4-o-Tolyl-pyridin-3-yl)-methanol (370 mg, 1.86 mmol), dissolved in 4 ml dimethyl formamide, was added dropwise and the mixture was stirred 1h at room temperature. 3,5-Bis(trifluoromethyl)benzyl bromide (627 mg, 2.04 mmol, 1 eq), dissolved in 2 ml dimethyl formamide, was added and the mixture was stirred 2.5h at room temperature.

[0124] The mixture was concentrated and the residue was partitioned between water and dichloromethane. The organic extract was washed with brine, dried (sodium sulfate), filtered, concentrated and purified by flash chromatography to give 196 mg (25%) of the title compound as yellow oil.

[0125] Starting material (0.24 g, 65%) was recovered.

MS m/e (%): 426 ($M+H^+$, 100)

Example 41

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-naphthalen-1-yl-nicotinamide hydrochloride (1:2)

[0126] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide (Example 12) using 1-naphthylboronic acid instead of o-tolylboronic acid in step d) and using N-methyl-6-(4-methyl-piperazin-1-yl)-4-naphthalen-1-yl-nicotinamide instead of N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in step e).

MS m/e (%): 587 ($M+H^+$, 100).

Example 42

(3,5-Bis-trifluoromethyl-benzyl)-[4-(2-chloro-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-ylmethyl]-methyl-amine; hydrochloride (1:3)

[0127] To a solution of 260 mg (0.455 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-4-(2-chloro-phenyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-nicotinamide (Example 13) in 6.3 ml dry tetrahydrofuran were added 2.73 ml (2.73 mmol) 1M borane solution in tetrahydrofuran. The mixture was heated at reflux for 16h. After cooling to room temperature 12.6 ml 3N hydrogen chloride solution in diethyl ether were added, and the mixture was heated at reflux for 40 min. After cooling to room temperature 1N aqueous sodium hydroxide solution was added. Extraction with ethyl acetate, drying with sodium sulfate and concentration were followed by flash chromatography affording 165 mg of a colorless oil. To a solution of the oil in 2 ml diethyl ether were added 3 ml 3N hydrogen chloride solution in diethyl ether. After stirring the mixture for 45 min. precipitate had formed which was collected by filtration. Drying in vacuo afforded 144 mg (47.5%) of the title compound as a white solid.

MS m/e (%): 557 ($M+H^+$, 100).

Example 43

4-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester

a) 6-Chloro-N-methyl-4-o-tolyl-nicotinamide

[0128] To a solution of 3.41 g (20.0 mmol) 6-chloro-N-methyl-nicotinamide (Example 12 step a)) in 80 ml tetrahydrofuran 50 ml (50 mmol) of a 1 M solution of o-tolyl magnesium chloride in tetrahydrofuran was added dropwise at 0 °C. After completed addition the reaction mixture was allowed to warm to room temperature and stirred for 1.5h. The mixture was again cooled to 0 °C, followed by the dropwise addition of 5.7 ml (100 mmol) acetic acid and a solution of 5.1 g (22 mmol) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 18 ml tetrahydrofuran. After completed addition the reaction mixture was allowed to warm to room temperature and stirred for 15 min. Addition of 30 ml 2 N aqueous sodium hydroxide solution was followed by dilution with 1l ethyl acetate and 200 ml water. The layers were separated and the organic layer was washed with 4 250-ml portions of 2 N aqueous sodium hydroxide solution. The combined aqueous layers were extracted with 3 500-ml portions of ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium chloride solution and dried with sodium sulfate. Concentration gave 5.44 g of a brown-red oil. Flash column chromatography afforded 2.15 g (41.3%) of the title compound as a light yellow solid.

MS m/e (%): 260 (M^+, 11), M.p. 91 - 93°C.

b) 4-(5-Methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

[0129] A mixture of 8.31 g (31.9 mmol) 6-chloro-N-methyl-4-o-tolyl-nicotinamide, 6.53 g (35.0 mmol) 1-tert-butoxycarbonyl piperazine, 16.7 ml (95.6 mmol) N-ethyldiisopropylamine and a catalytic amount of 4-(N,N-dimethylamino)-pyridine was heated at reflux over night. After cooling to room temperature the mixture was dissolved in dichlorometh-

ane and washed with two portions of 0.1 N aqueous hydrochloric acid solution. Drying with sodium sulfate and concentration gave 10.7 g of the crude product. Flash column chromatography afforded 6.28 g (48.0%) of the title compound as an off-white solid.

MS m/e (%): 411 ($M+H^+$, 100).

c) 4-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester

[0130] The title compound was obtained as a white solid in comparable yield according to the procedure described above for the preparation of N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide (Example 12, step e)) using 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester instead of N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide.

MS m/e (%): 637 ($M+H^+$, 100).

Example 44

(4-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazin-1-yl)-acetic acid ethyl ester

[0131] The title compound was obtained as a yellow solid in comparable yield for step b) and 3% yield for step c) according to the procedures described above for the preparation of 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43) using 1-(ethoxycarbonylmethyl)-piperazine instead of 1-tert-butoxycarbonyl piperazine in step b) and using [4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazin-1-yl]-acetic acid ethyl ester instead of 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in step c).

MS m/e (%): 623 ($M+H^+$, 100).

Example 45

5'-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester

[0132] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43) using ethyl isonipecotate instead of 1-tert-butoxycarbonyl piperazine in step b) and using 5'-methylcarbamoyl-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-4-carboxylic acid ethyl ester instead of 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in step c).

MS m/e (%): 608 ($M+H^+$, 100).

Example 46

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-propyl-piperazin-1-yl)-4-o-tolyl-nicotinamide

[0133] The title compound was obtained as a light-yellow solid in comparable yields according to the procedures described above for the preparation of 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43) using 1-propyl piperazine instead of 1-tert-butoxycarbonyl piperazine in step b) and using N-methyl-6-(4-propyl-piperazin-1-yl)-4-o-tolyl-nicotinamide instead of 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in step c).

MS m/e (%): 579 ($M+H^+$, 100).

Example 47

(RS)-6-[3-(Acetyl-methyl-amino)-pyrrolidin-1-yl]-N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide

[0134] The title compound was obtained as a light-yellow solid in comparable yields according to the procedures described above for the preparation of 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43) using (RS)-3-(acetyl-methyl-amino)-pyrrolidine instead of 1-tert-butoxycarbonyl piperazine in step b) and using (RS)-6-[3-(acetyl-methyl-amino)-pyrrolidin-1-yl]-N-methyl-4-o-tolyl-nicotinamide instead of 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in step c).

MS m/e (%): 593 ($M+H^+$, 100).

Example 48

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-nicotinamide

[0135] The title compound was obtained as a light-yellow solid in comparable yields according to the procedures described above for the preparation of 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43) using methyl-(2-morpholin-4-yl-ethyl)-amine instead of 1-tert-butoxycarbonyl piperazine in step b) and using N-methyl-6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-nicotinamide instead of 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in step c).

MS m/e (%): 595 ($M+H^+$, 100).

Example 49

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0136] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43) using morpholine instead of 1-tert-butoxycarbonyl piperazine in step b) and using N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide instead of 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in step c).

MS m/e (%): 538 ($M+H^+$, 100).

Example 50

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-thiomorpholin-4-yl-4-o-tolyl-nicotinamide

[0137] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43) using thiomorpholine instead of 1-tert-butoxycarbonyl piperazine in step b) and using N-methyl-6-thiomorpholin-4-yl-4-o-tolyl-nicotinamide instead of 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in step c).

MS m/e (%): 554 ($M+H^+$, 100).

Example 51

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(1-oxo-1λ^4-thiomorpholin-4-yl)-4-o-tolyl-nicotinamide

[0138] To a solution of 1.24 g (2.24 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-thiomorpholin-4-yl-4-o-tolyl-nicotinamide (Example 50) in 25 ml methanol were added 689 mg (1.12 mmol) Oxone® at 0°C. After completed addition the reaction mixture was allowed to warm to room temperature and stirred for 1.5h. Quenching with 5 ml 40% aqueous sodium hydrogen sulfite solution was followed by addition of 6 ml 1N sodium hydroxide solution to adjust the

pH to 7-8. The mixture was diluted with 50 ml water and extracted with 3 150-ml portions of dichloromethane. The combined extracts were dried with sodium sulfate and concentrated to give 1.20 g of crude product. Flash chromatography afforded 1.02 g (79.9%) of the title compound as a white solid.

MS m/e (%): 570 ($M+H^+$, 100).

Example 52

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-N-methyl-4-o-tolyl-nicotinamide

[0139] The title compound was obtained as a white solid in comparable yield according to the procedure described above for the preparation of N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(1-oxo-1l 4-thiomorpholin-4-yl)-4-o-tolyl-nicotinamide (Example 51) using N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(1-oxo-1l 4-thiomorpholin-4-yl)-4-o-tolyl-nicotinamide instead of N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-thiomorpholin-4-yl-4-o-tolyl-nicotinamide.

MS m/e (%): 586 ($M+H^+$, 100).

Example 53

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide

[0140] To a solution of 6.60 g (104 mmol) 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43) and 8.40 ml (207 mmol) methanol in 50 ml ethyl acetate 14.7 ml (207 mmol) acetyl chloride were added dropwise at 0 °C. After 4h the reaction mixture was diluted with ethyl acetate and treated with 1 N sodium hydroxide solution. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic layers were dried with sodium sulfate and concentrated to give 5.36 g of crude product. Flash column chromatography afforded 4.86 g (87.4%) of the title compound as a light brown solid.

MS m/e (%): 537 ($M+H^+$, 100).

Example 54

N-(3,5-Bis-trifluoromethyl-benzyl)-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-N-methyl-4-o-tolyl-nicotinamide

[0141] A mixture of 100 mg (0.186 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide (Example 53), 0.030 ml (0.42 mmol) 2-bromo-ethanol and 46 mg (0.33 mmol) potassium carbonate in 2 ml acetonitrile was stirred at 45 °C for 70h. After cooling to room temperature 10 ml 1 N sodium hydroxide solution were added. Extraction with 3 15-ml portions of ethyl acetate, drying with sodium sulfate and concentration gave 138 mg of the crude product. Flash column chromatography afforded 85 mg (78.6%) of the title compound as a white solid.

MS m/e (%): 581 ($M+H^+$, 100).

Example 55

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-cyanomethyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide

[0142] The title compound was obtained as a white solid in comparable yield according to the procedure described above for the preparation of N-(3,5-bis-trifluoromethyl-benzyl)-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-N-methyl-4-o-tolyl-nicotinamide (Example 54) using chloro-acetonitrile instead of 2-bromo-ethanol.

MS m/e (%): 576 ($M+H^+$, 100).

Example 56

N-(3,5-Bis-trifluoromethyl-benzyl)-6-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-N-methyl-4-o-tolyl-nicotinamide

[0143] A mixture of 400 mg (0.746 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-

nicotinamide (Example 53), 0.18 ml (1.7 mmol) 2-(2-chloroethoxy)-ethanol and 0.189 g (1.35 mmol) potassium carbonate in 8 ml acetonitrile was stirred at 85 °C for 48h. After cooling to room temperature 40 ml 1 N sodium hydroxide solution were added. Extraction with 3 60-ml portions of dichloromethane, drying with sodium sulfate and concentration gave 528 mg of the crude product. Flash column chromatography afforded 300 mg (64.4%) of the title compound as a light-brown solid.

MS m/e (%): 625 ($M+H^+$, 100).

Example 57

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-[1,2,4] oxadiazol-3-ylmethyl-piperazin-1-yl)-4-o-tolyl-nicotinamide

[0144] A mixture of 200 mg (0.373 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide (Example 53), 66 mg (0.56 mmol) 3-(chloromethyl)-1,2,4-oxadiazole and 62 mg (0.45 mmol) potassium carbonate in 4 ml acetonitrile was stirred at 45 °C for 1h and at room temperature over night. The reaction mixture was diluted with 10 ml water and extracted with 3 30-ml portions of dichloromethane. Drying with sodium sulfate and concentration gave 244 mg of the crude product. Flash column chromatography afforded 80 mg (34.7%) of the title compound as a red-brown solid.

MS m/e (%): 619 ($M+H^+$, 100).

Example 58

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[4-(5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-ylmethyl)-piperazin-1-yl]-4-o-tolyl-nicotinamide

[0145] A mixture of 800 mg (1.49 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide (Example 53), 296 mg (1.79 mmol) N-carbomethoxy-2-chloroacetamidrazone and 0.52 ml (3.0 mmol) N-ethyl-diisopropylamine in 14 ml acetonitrile was stirred at room temperature for 2h. The reaction mixture was diluted with 20 ml water and extracted with 3 50-ml portions of dichloromethane. The combined extracts were dried with sodium sulfate and concentrated. The residue was dissolved in 14 ml DMF, and 0.29 ml (1.6 mmol) N-ethyl-diisopropylamine were added. The reaction mixture was stirred at 140 °C over night. Concentration and drying in high vacuo gave 1.09 g of crude product. Flash column chromatography afforded 820 mg (86.8%) of the title compound as a light-brown solid.

MS m/e (%): 634 ($M+H^+$, 100).

Example 59

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-formyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide

[0146] To a mixture of 0.089 ml (1.1 mmol) N,N-dimethylformamide and 38 mg (0.56 mmol) imidazole 0.071 ml (0.56 mmol) trimethylchlorosilane were added dropwise at room temperature. The reaction mixture was cooled to 0°C, and 0.10 g (0.19 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide (Example 53)were added. The ice-water bath was removed and the mixture stirred over night. The reaction was quenched with a mixture of 2 ml 1 N aqueous hydrochloric acid solution and 4 ml water, and the mixture was extracted with ethyl acetate. The combined extracts were dried with sodium sulfate and concentrated. Flash column chromatography afforded 81 mg (82%) of the title compound as a white solid.

MS m/e (%): 565 ($M+H^+$, 100).

Example 60

N-Methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide

a) N-Methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0147] The title compound was obtained as an off-white solid in comparable yield according to the procedure

described above for the preparation of 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester (Example 43, step b) using morpholine instead of 1-tert-butoxycarbonyl piperazine.

MS m/e (%): 311 (M^+, 63).

b) N-Methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0148] The title compound was obtained as a white solid in comparable yield according to the procedure described above for the preparation of N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 12, step e)) using 1-chloromethyl-2-methylnaphthalene instead of 3,5-bis-trifluoromethyl-benzyl bromide.

MS m/e (%): 466 ($M+H^+$, 100).

Example 61

N-Methyl-6-morpholin-4-yl-N-naphthalen-1-ylmethyl-4-o-tolyl-nicotinamide

[0149] The title compound was obtained as a colorless viscous oil in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using 1-chloromethylnaphthalene instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 452 ($M+H^+$, 100).

Example 62

N-(2-Methoxy-naphthalen-1-ylmethyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0150] The title compound was obtained as a colorless viscous oil in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using toluene-4-sulfonic acid 2-methoxy-naphthalen-1-ylmethyl ester instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 482 ($M+H^+$, 100).

Example 63

N-(2-Methoxy-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0151] The title compound was obtained as a colorless viscous oil in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using 2-methoxy-benzyl chloride instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 432 ($M+H^+$, 100).

Example 64

N-(5-Chloro-2-methoxy-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0152] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using 5-chloro-2-methoxy-benzyl chloride instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 466 ($M+H^+$, 100).

Example 65

N-(2-Chloro-5-methoxy-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0153] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using 2-chloro-5-methoxy-benzyl bromide instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 466 ($M+H^+$, 100).

Example 66

N-Methyl-6-morpholin-4-yl-N-pentafluorophenylmethyl-4-o-tolyl-nicotinamide

[0154] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using 2,3,4,5,6-pentafluoro-benzyl bromide instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 492 ($M+H^+$, 100).

Example 67

N-Methyl-6-morpholin-4-yl-N-naphthalen-2-ylmethyl-4-o-tolyl-nicotinamide

[0155] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using 2-chloromethyl-naphthalene instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 452 ($M+H^+$, 100).

Example 68

N-[2-Methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0156] The title compound was obtained as a white solid in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using toluene-4-sulfonic acid [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-phenyl]-methyl ester instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 568 ($M+H^+$, 100).

Example 69

N-(1,4-Dimethoxy-naphthalen-2-ylmethyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide

[0157] The title compound was obtained as a colorless viscous oil in comparable yields according to the procedures described above for the preparation of N-methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide (Example 60) using 2-chloromethyl-1,4-dimethoxy-naphthalene instead of 1-chloromethyl-2-methylnaphthalene in step b).

MS m/e (%): 512 ($M+H^+$, 100).

Example 70

5'-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid

[0158] A mixture of 200 mg (0.33 mmol) 5'-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester (Example 45), 10 ml 1N aqueous sodium hydroxide solution and 10 ml methanol was stirred at room temperature over night. After washing with 2 portions of ethyl acetate the aqueous layer was acidified to pH 4 with 1N aqueous hydrochloric acid solution. Extraction with dichloromethane, drying with sodium sulfate and flash column chromatography afforded 81 mg (42%) of the title compound as a white solid.

MS m/e (%): 580 ($M+H^+$, 100).

Example 71

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[4-(1H-tetrazol-5-ylmethyl)-piperazin-1-yl]-4-o-tolyl-nicotinamide

[0159] A mixture of 0.10 g (0.17 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-cyanomethyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide (Example 55), 34 mg (0.52 mmol) sodium azide and 36 mg (0.26 mmol) triethylammonium chloride in 1 ml 1-methyl-2-pyrrolidone was heated at reflux for 2h. After cooling to room temperature 6 ml ice water were added. The mixture was acidified with 1N hydrochloric acid solution to pH 1-2 and extracted with dichloromethane. Drying of the combined extracts with sodium sulfate, concentration and flash column chromatography afforded 95 mg (88%) of the title compound as a light brown solid.

MS m/e (%): 619 ($M+H^+$, 100).

Example 72

N-(6-Benzylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

a) 2-Benzyl-N5-methyl-4-o-tolyl-pyridine-2,5-diamine

[0160] The title compound was prepared following the procedures described above for the synthesis of methyl-6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine (Example 23, step f).

MS m/e (%): 304 ($M+H^+$, 100).

b) Benzyl-(5-methylamino-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester

[0161] To a solution of 2.03 g (6.7 mmol) N2-benzyl-N5-methyl-4-o-tolyl-pyridine-2,5-diamine in 100 ml dichloromethane and 40 ml N-ethyldiisopropylamine was added dropwise at 0°C a solution of 2.1 ml (14.09 mmol) benzyl chloroformate in 50 ml dichloromethane. After stirring for 2h at room temperature the reaction mixture was washed with water (2 x 50 ml), brine (50 ml), dried (magnesium sulfate) and evaporated. Chromatography of the residue afforded 2.36 g (80%) of the title compound as light brown crystals. M.p. 110-112°C.

MS m/e (%): 438 ($M+H^+$, 100).

c) Benzyl-(5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester

[0162] To a solution of 1.075 g (2.5 mmol) benzyl-(5-methylamino-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester in 10 ml dichloromethane and 1 ml N-ethyldiisopropylamine was added dropwise at 0°C a solution of 1.15 g (3.5 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid chloride in 2 ml dichloromethane and the mixture was stirred for 3h at room temperature. The solution was washed with water (20 ml), saturated aqueous sodium hydrogencarbonate solution (20 ml) and brine (20 ml), dried (magnesium sulfate) and evaporated. Chromatography of the residue afforded 1.15 g (62%) of the title compound as a yellow oil.

MS m/e (%): 720 ($M+H^+$, 100).

d) N-(6-Benzylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

[0163] To a solution of 973 mg (1.35 mmol) benzyl-(5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester in 13 ml methanol and 1 ml N,N-dimethylformamide was added 40 mg 10% palladium on activated charcoal and the mixture was hydrogenated (room temperature, 1 bar) for 1h. Filtration of the catalyst and evaporation of the filtrate afforded 795 mg (quantitative) of the title compound as a yellow oil.

MS m/e (%): 586 ($M+H^+$, 100).

Example 73

N-(6-Amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

[0164] A solution of 750 mg (1.28 mmol) N-(6-benzylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide (Example 73, step d) in 25 ml of a 5 N solution of hydrochloric acid in ethanol was evaporated to dryness and the residue was dissolved in 30 ml methanol and hydrogenated in the presence of 60 mg 10% palladium on activated charcoal (room temperature, 10 bar) for 20h. After filtration of the catalyst and evaporation of the solvent the residue was dissolved in 30 ml ethyl acetate, washed twice with saturated aqueous sodium hydrogencarbonate solution and dried (magnesium sulfate). Evaporation of the solution afforded 514 mg (81%) of the title compound as light brown crystals.

MS m/e (%): 496 ($M+H^+$, 100).

Example 74

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(dimethylamino-methyleneamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

[0165] To a solution of 100 mg (0.2 mmol) N-(6-amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide (Example 73) in 4 ml N,N-dimethylformamide was added at 0°C 11 mg (0.252 mmol) sodium hydride as a 60% dispersion in oil and the mixture was stirred for 30 min without cooling. Then 28 ul (0.218 mmol) benzenesulfonyl chloride were added at 0°C and the solution was stirred over night at room temperature. The reaction mixture was added to water and extracted with ethyl acetate (3 x 10 ml). The combined extracts were washed with water (3 x 20 ml), brine (20 ml), dried (magnesium sulfate) and evaporated. Chromatography of the residue afforded 51 mg (46%) of the title compound as a white foam.

MS m/e (%): 551 ($M+H^+$, 100).

Example 75

2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-methanesulfonylamino-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide

[0166] To a solution of 100 mg (0.2 mmol) N-(6-amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide i(Example 73) in 2 ml pyridine were added 27 ul (0.35 mmol) methanesulfonyl chloride and the mixture was stirred over night at room temperature. After evaporation of the solvent the residue was dissolved in ethyl acetate, washed twice with saturated aqueous sodium hydrogencarbonate solution, brine and dried (magnesium sulfate). Chromatography of the residue afforded 24 mg (42%) of the title compound as a white foam.

MS m/e (%): 574 ($M+H^+$, 100).

Example 76

N-(6-Benzenesulfonylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

[0167] To a solution of 100 mg (0.2 mmol) N-(6-amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 4 ml dichloromethane and 85 ul N-ethyldiisopropylamine were added 56 ul (0.436 mmol) benzenesulfonyl chloride and the mixture was stirred over night at room temperature. The reaction mixture was washed

twice with saturated aqueous sodium hydrogencarbonate solution and dried (magnesium sulfate). Chromatography of the residue afforded 26 mg (28%) of the title compound as a white foam.

MS m/e (%): 634 ($M-H^+$, 100).

Example A

[0168] Tablets of the following composition are manufactured in the usual manner:

	mg/tablet
Active substance	5
Lactose	45
Corn starch	15
Microcrystalline cellulose	34
Magnesium stearate	1
	Tablet weight 100

Example B

Capsules of the following composition are manufactured:

[0169]

	mg/capsule
Active substance	10
Lactose	155
Corn starch	30
Talc	5
	Capsulefill weight 200

[0170] The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

Example C

Suppositories of the following composition are manufactured:

[0171]

	mg/supp.
Active substance	15

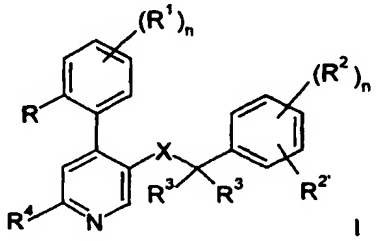
(continued)

	mg/supp.
Suppository mass	1285
	Total 1 300

[0172] The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

Claims

1. Compounds of the general formula

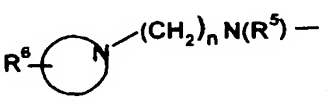


I

wherein

R	is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;
R^1	is hydrogen or halogen; or
R and R^1	may be together -CH=CH-CH=CH-;
R^2 and $R^{2'}$	are independently from each other hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano; or
R^2 and $R^{2'}$	may be together -CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl or lower alkoxy;
R^3	is hydrogen, lower alkyl or form a cycloalkyl group;
R^4	is hydrogen, $-N(R^5)_2$, $-N(R^5)(CH_2)_nOH$, $-N(R^5)S(O)_2$-lower alkyl, $-N(R^5)S(O)_2$-phenyl, $-N{=}CH-N(R^5)_2$, $-N(R^5)C(O)R^5$ or a cyclic tertiary amine of the group

or the group



;

R^5 is, independently from each other, hydrogen, C_{3-6}-cycloalkyl, benzyl or lower alkyl;

R^6 is hydrogen, hydroxy, lower alkyl, $-(CH_2)_nCOO$-lower alkyl, $-N(R^5)CO$-lower alkyl, hydroxy-lower alkyl, cyano, $-(CH_2)_nO(CH_2)_nOH$, -CHO or a 5-or 6 membered heterocyclic group, optionally bonded via an alkylene group,

X is $-C(O)N(R^5)-$, $-(CH_2)_mO-$, $-(CH_2)_mN(R^5)$, $-N(R^5)C(O)-$, or $-N(R^5)(CH_2)m-$;

n is 0 - 4; and

m is 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

2. A compound according to claim 1, wherein X is $-C(O)N(R^5)-$ and R^5 is methyl, ethyl or cyclopropyl.

3. A compound according to claim 2, which is

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-chloro-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-trifluoromethyl-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-fluoro-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-(2-methoxy-phenyl)-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-phenyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-ethyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-cyclopropyl-4-o-tolyl-nicotinamide,
N-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Di-fluorobenzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Di-chlorobenzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
2'-Methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-2-carboxylic acid-(3,5-bis-trifluoro-methyl-benzyl)-methyl-amide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-methyl-piperazin-1-yl)-4-naphthalen-1-yl-nicotinamide,
(4-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazin-1-yl)-acetic acid ethyl ester,
5'-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-propyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
(RS)-6-[3-(Acetyl-methyl-amino)-pyrrolidin-1-yl]-N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-morpholin-4-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-thiomorpholin-4-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(1-oxo-1l 4-thiomorpholin-4-yl)-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-cyanomethyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-(4-[1,2,4] oxadiazol-3- ylmethyl-piperazin-1-yl)-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-[4-(5-oxo-4,5-dihydro-1H-[1,2,4] triazol-3-ylmethyl)-piperazin-1-yl]-4-o-tolyl-nicotinamide,
N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-formyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide and
N-Methyl-N-(2-methyl-naphthalen-1-ylmethyl)-6-morpholin-4-yl-4-o-tolyl-nicotinamide.

4. A compound according to claim 1, wherein X is -N(R^5)C(O)- and R^5 is hydrogen or methyl.

5. A compound according to claim 4, which is

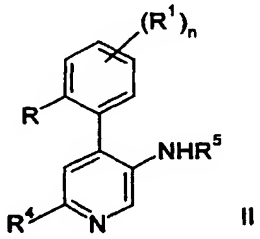
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-acetamide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(4-o-tolyl-pyridin-3-yl)-propionamide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-morpholin-4-yl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-{6-[methyl-(2-morpholin-4-yl-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-pyrimidin-2-yl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-(2-chloro-phenyl)-6-dimethylamino-pyridin-3-yl]-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-piperazin-1-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-(4-hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-5'-yl)-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-{6-[(2-hydroxy-ethyl)-methyl-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide,
(R)-2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-acetamide and
[2-(3,5-Bis-trifluoromethyl-phenyl)-2-methyl-propyl]-[4-(4-fluoro-2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-methyl-amine.

6. A medicament containing one or more compounds as claimed in any one of claims 1-5 and pharmaceutically acceptable excipients.

7. A medicament according to claim 6 for the treatment of diseases related to NK- 1 receptor antagonists.

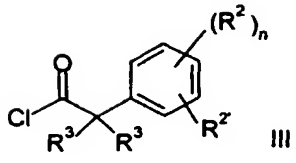
8. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



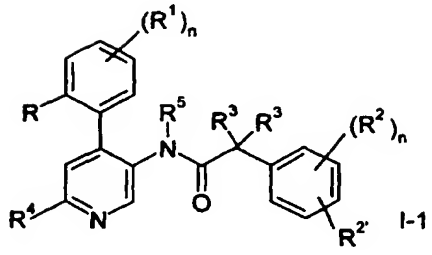
II

with a compound of formula



III

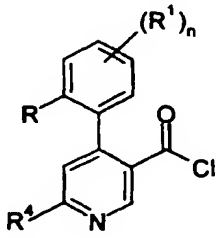
to a compound of formula



I-1

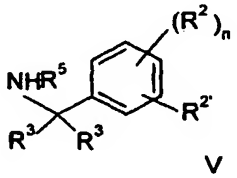
wherein R^1- R^5, R and n have the significances given above, or

b) reacting a compound of formula



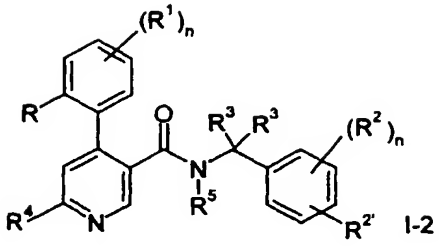
IV

with a compound of formula



V

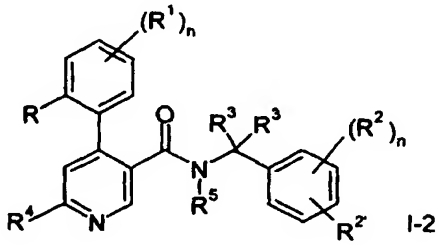
to give a compound of formula



I-2

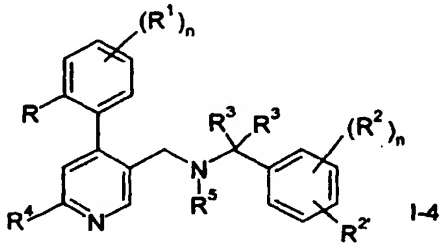
wherein R^1-R^5, R and n have the significances given above, or

c) reducing a compound of formula



I-2

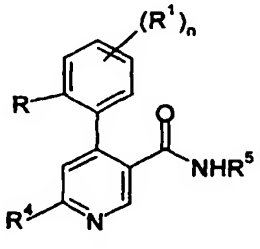
to a compound of formula



I-4

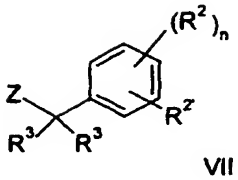
wherein the definition of substituents is given above, or

d) reacting a compound of formula



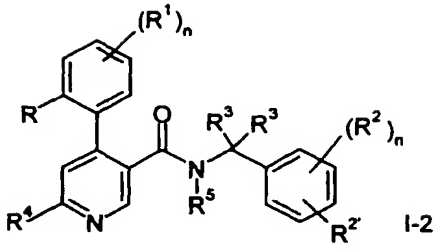
VI

with a compound of formula



VII

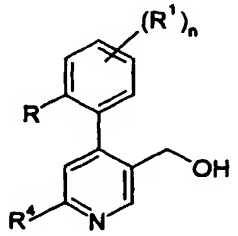
to a compound of formula



I-2

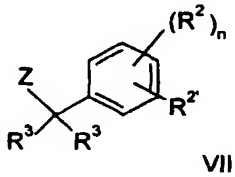
wherein Z is Cl, Br, I or $-OS(O)_2C_6H_4CH_3$ and the definition of further substituents is given above, or

e) reacting a compound of formula



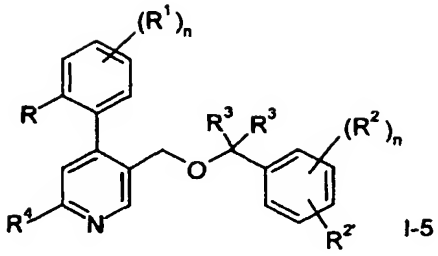
VIII

with a compound of formula



VII

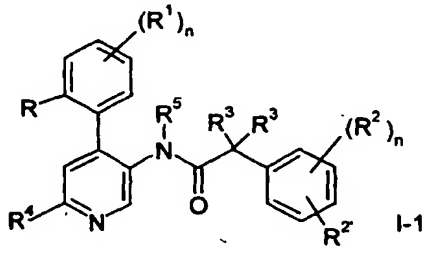
to a compound of formula



I-5

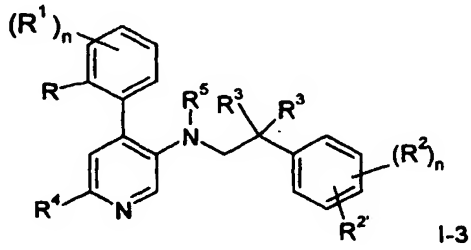
wherein Z is Cl, Br, I or $-OS(O)_2C_6H_4CH_3$ and the definition of the other substituents is given above, or

f) reducing a compound of formula



I-1

to a compound of formula



I-3

wherein the definition of substituents is given above,
or

h) modifying one or more substituents R^1-R^6 or R within the definitions given above, and if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

9. A compound according to any one of claims 1-5, whenever prepared by a process as claimed in claim 8 or by an equivalent method.

10. The use of a compound in any one of claims 1-5 for the treatment of diseases related to NK- 1 receptor antagonists.

11. The use of a compound in any one of claims 1-5 for the manufacture of medicaments containing one or more compounds of formula I for the treatment of diseases related to NK- 1 receptor antagonists.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 00 10 2260

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	IKEURA, YOSHINORI ET AL: "Potent NK1 receptor antagonists: synthesis and antagonistic activity of various heterocycles with an N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoyl substituent" CHEM. PHARM. BULL. (1997), 45(10), 1642-1652 , XP000910111 * page 1647; tables 1,2 * * reference [25] * ---	1-11	C07D213/82 C07D213/75 C07D401/12 C07D401/04 C07D213/74 C07D213/38 C07D213/30 C07D413/12 A61P25/00 A61P29/00 A61K31/44 A61K31/455 A61K31/4427
A	EP 0 733 632 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 25 September 1996 (1996-09-25) * claims 1,25,28 * --- -/--	1-11	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07D

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claim 10 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
MUNICH	30 May 2000	Seymour, L

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 10 2260

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	NATSUGARI, HIDEAKI ET AL: "Novel, Potent, and Orally Active Substance P Antagonists: Synthesis and Antagonist Activity of N-Benzylcarboxamide Derivatives of Pyrido[3,4-b]pyridine" JOURNAL OF MEDICINAL CHEMISTRY., vol. 38, no. 16, 1995, pages 3106-3120, XP000910106 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 * tables 2,3 * ---	1-11	
X	EP 0 235 663 A (WARNER-LAMBERT CO., USA) 9 September 1987 (1987-09-09) * page 11, formula 7 * * page 10, line 25-28 * * page 40; example 46A * -----	1,8,9	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 10 2250

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

30-05-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0733632 A	25-09-1996	AU 699611 B	10-12-1998
		AU 4826196 A	03-10-1996
		BR 9601125 A	06-01-1998
		CA 2172421 A	25-09-1996
		CN 1140172 A	15-01-1997
		HU 9600732 A	28-03-1997
		JP 9263587 A	07-10-1997
		JP 2976097 B	10-11-1999
		JP 9263585 A	07-10-1997
		NO 961160 A	25-09-1996
		NZ 286256 A	28-05-1999
		US 5786352 A	28-07-1998
		US 5770590 A	23-06-1998
EP 0235663 A	09-09-1987	US 4745123 A	17-05-1988
		AT 54910 T	15-08-1990
		CA 1285939 A	09-07-1991
		DE 3763863 D	30-08-1990
		GR 3000682 T	27-09-1991
		JP 2117641 C	06-12-1996
		JP 8032682 B	29-03-1996
		JP 62192358 A	22-08-1987

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82